OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW

NDA	208464/S-14 [redacted]
Submission dates	04/19/2022 05/27/2022 (IR response) 06/22/2022 (IR response) 08/26/2022 (IR response) 09/14/2022 (IR response)
Submission type	Pediatric efficacy supplement
Drug, Dosage Form, Strength	Vemlidy® (Tenofovir Alafenamide; TAF), Tablets, 25 mg
Applicant	Gilead Sciences, Inc.
Proposed Indication	Treatment of Chronic Hepatitis B (CHB) virus infection in pediatric patients [redacted] with compensated liver disease
OCP Division	DIDP
OND Division	DAV
Review Team	Yang Zhao, Ph.D.; Abhay Joshi, Ph.D. Jiajun Liu, Pharm.D, MSc; Justin Earp, Ph.D.

1 Executive Summary

Vemlidy® (Tenofovir Alafenamide; TAF) 25 mg tablet was approved by the FDA on 11/10/2016 for the treatment of chronic hepatitis B virus infection (CHB) with compensated liver disease in adults. The applicant submitted this efficacy supplement (S-14) to expand the use of Vemlidy® in pediatric patients [redacted] with compensated liver disease. The approved dosing regimen in adults is 25 mg once daily. The applicant has proposed the same dosing regimen in pediatric patients [redacted]

The Applicant submitted the following study/analysis reports [redacted]

- Interim week 24 clinical study report (link) for the study GS-US-320-1092: A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection, including:
    - intensive TAF and tenofovir (TFV) PK data from 18 CHB pediatric subjects (13 subjects in Cohort 1 who are 12 to < 18 years of age and weighing ≥ 35 kg; 5 subjects in Cohort 2 Group 1 who are 6 to <12 years of age and weighing ≥ 25 kg)
    - sparse TAF and TFV PK data from the remaining 41 CHB pediatric subjects (34 subjects in Cohort 1; 7 subjects in Cohort 2 Group 1).
- Population pharmacokinetic (PopPK) analysis report supporting the proposed dosing regimen [redacted] (CTRA-2021-1058

TAF-TFV PopPK Ped) based on pharmacokinetic (PK) data from HIV-1 studies: GS-US-292-0106, GS-US-292-1515, GS-US-311-1269, GS-US-380-1474 and one CHB trial: GS-US-320-1092.

- A supplemental population PK simulation report (CTRA-2021-1061 TAF-TFV PopPK HBV Ped Sim).

To support dose selection and approval in pediatrics, the applicant relied on demonstrating similarity of TAF and TFV exposures observed in trial GS-US-320-1092 and in HIV-1 infected adults in the Genvoya® development program in order to extrapolate the efficacy of TAF from adults with CHB infection to pediatrics with CHB infection; however, the review team considered demonstration of similarity of TAF and TFV exposures observed in trial GS-US-320-1092 and the adult CHB patients as supportive evidence for efficacy, whereas the PK data from both indications (HIV-1 and CHB) as supportive evidence for safety. The exposure comparison findings were utilized as supportive evidence for efficacy due the reported differences in efficacy results between the younger (6 to < 12 years) and older (12 to <18 years) age cohorts in trial GS-US-320-1092. Specifically, at Week 24, 10/47 (21.3%) of subjects aged 12 to <18 years receiving Vemlidy® achieved viral suppression in terms of primary efficacy endpoint (proportion of subjects with plasma HBV DNA levels < 20 IU/mL) compared to none in the placebo group; however, only 1/12 (8.3%) of participants aged 6 to <12 years receiving Vemlidy® achieved viral suppression by Week 24 compared to none in the placebo group. (b) (4) [redacted]. Also, refer to virology review and clinical review for information on the differences in the baseline characteristics between two age groups.

Overall, PK assessment approaches including both noncompartmental analysis (NCA) and popPK analyses of TAF and TFV were utilized in evaluating their roles in providing supportive evidence for the dose selection rationale, safety, and efficacy. The Clinical Pharmacology Review Team determined that no meaningful differences were observed in TAF and TFV exposures for the proposed Vemlidy® oral dosage of 25 mg once daily for pediatric CHB patients 6 years of age and older compared to the respective exposures reported in CHB adult patients and HIV-1 adult patients receiving the same Vemlidy® dosage. See Section 3, Section 5.3, and clinical review for further details.

The primary basis of approval for the proposed Vemlidy® dosage for pediatric patients 12 to <18 years of age is the observed safety and efficacy data from 59 pediatric subjects from clinical trial GS-US-320-1092, which evaluated the Vemlidy® dosage regimen that is currently approved for adults (i.e., 25 mg orally once daily). The exposure comparison findings provide supportive evidence for efficacy and safety for the proposed Vemlidy® dosage for pediatric patients 12 to <18 years of age. (b) (4) [redacted]

Recommendations

For Supplement 14: The Review Team supports the approval of TAF in pediatric patients 12 to <18 years of age weighing at least 25 kg with compensated liver disease and agrees with updating the content of labeling with Week 24 data.

(b) (4)

2 Background

Vemlidy® is an immediate-release dosage form containing a single active ingredient, 25 mg of TAF as TAF fumarate. In the current submission, the Applicant proposes to expand the use of Vemlidy® for the treatment of CHB in pediatric patients (b) (4) TAF is a prodrug of the nucleotide reverse transcriptase inhibitor, tenofovir (TFV). TFV undergoes intracellular phosphorylation to form the active metabolite, TFV diphosphate (TFV-DP), in target cell to inhibit viral DNA replication.

TAF has been also approved by the FDA for the treatment of human immunodeficiency virus type 1 (HIV-1) infections in adults and pediatrics (weighing at least 25 kg) as a part of various Fixed-Dose Combination (FDC) products, including Biktarvy® (bictegravir, emtricitabine, and TAF) (NDA-210251), Descovy® (emtricitabine and TAF) (NDA-208215), and Genvoya® (elvitegravir, cobicistat, emtricitabine, and TAF) (NDA-207561).

3 Summary of Clinical Pharmacology Assessments

In addition to the observed safety and efficacy data from trial GS-US-320-1092, the following clinical pharmacology assessments provide supportive evidence for safety and efficacy:

1. TAF and TFV exposure in CHB pediatrics receiving the proposed Vemlidy® regimen was compared with the following adult patient groups:
    a. CHB adult patients receiving the same Vemlidy® regimen currently approved (as supportive evidence for efficacy and safety)
    b. HIV-1 adult patients who received a fixed-dose combination of elvitegravir/cobicistat/emtricitabine/TAF (Genvoya®) (as supportive evidence for safety)
2. Exposure-response analyses for safety and efficacy findings in CHB pediatric patients
3. Dosage recommendation for CHB adolescent patients with impaired renal function

The clinical pharmacology review of the abovementioned three aspects is summarized in the next sub-sections. Overall, the TAF and TFV exposures showed no clinically meaningful differences between CHB pediatric patients 6 years of age and older when compared to the exposures reported in CHB adult patients receiving the proposed Vemlidy® dosage of 25 mg taken orally once daily or exposures in HIV-1 adult patients who received the recommended dose of Genvoya®. Further, exposure-response analyses did not identify any correlation between TAF or TFV exposure-response relationships for efficacy or safety at Week 24. Collectively, the proposed dosing regimen of Vemlidy® 25 mg once daily (same as the approved adult dosing regimen) in CHB pediatric patients 12 to <18 years of age is appropriate from a clinical pharmacology perspective. (b) (4)

3.1 TAF and TFV exposure comparison between pediatrics (6 to < 18 years) and adults

TAF and TFV exposure comparisons between CHB pediatric patients, CHB adult patients, and HIV-1 adult patients receiving the proposed Vemlidy® regimen or comparable TAF regimen (for HIV-1 patients) were performed using both intensive and sparse PK data. Specifically, an NCA approach was used with intensive PK data to compare TAF and TFV exposure between CHB pediatric patients (who received the proposed Vemlidy® dosing regimen, n=18) and CHB adult patients (who received the currently approved Vemlidy dosing regimen, n=8) (Table 1). A popPK based approach was utilized to compare the posterior-predicted TAF and TFV exposure between CHB pediatric patients (receiving the proposed Vemlidy® dosing regimen, n=59) and HIV-1 patients (who received Genvoya®) (Table 2).

As shown in Table 1, TAF AUCtau estimates from intensive PK data in CHB pediatric patients were comparable (approximately <16% difference) to historical data in CHB adults. TAF Cmax estimates were approximately 30% lower in Cohort 1 and 44% higher in Cohort 2 Group 1, when compared to historical adult data. Despite the observed 30% lower TAF Cmax in Cohort 1, the interim efficacy rate in this age group was higher compared to Cohort 2 Group 1 that had reported 44% higher Cmax compared to adults. The observed 44% higher TAF Cmax observed in Cohort 2 Group 1 is not considered clinically relevant as TAF exposures were not found to be related to safety findings (See Reviewer's Comments under Section 5.2 and exposure-response analysis in Section 5.3.3). When comparing popPK model derived exposure metrics for 59 CHB pediatric patients to historical HIV-1 adults in Table 2, Cohort 1 of the pediatric population showed similar TAF exposure while Cohort 2 Group 1 had numerically lower (~15% in terms of AUCtau) TAF exposures to the reference adult population.

For TFV exposures, based on comparison of intensive PK data, both pediatric cohorts had lower (~49% for Cohort 1, ~ 38% for Cohort 2 Group 1 in terms of AUCtau) TFV exposure when compared to those of the CHB adults. When comparing popPK model derived TFV exposures,

Cohort 1 had lower (~14% in terms of AUCtau) TFV exposures while Cohort 2 showed comparable TFV exposures to the reference adult population. Refer to details on exposure comparison between CHB pediatric and HIV-1 adult subjects based on simulation in Section 5.3.2. The available data suggest that lower TFV exposure in CHB pediatric subjects are not considered clinically relevant based on the following:

- Within the available limited data, there is a lack of apparent visual relationship for TFV exposure and HBV DNA outcome (<20 IU/mL) by study cohorts (Section 5.3.3)
- An exploratory analysis suggested that there is no apparent relationship identified between exposures (TAF or TFV) and HBV DNA reduction from base line (Section 5.2)

Overall, the review team considered that drug exposures (AUCtau and Cmax for TAF; AUCtau, Cmax, and Ctau for TFV) of the proposed Vemlidy® oral dosage of 25 mg once daily in CHB pediatric patients of interest have no meaningful differences to the respective exposures in CHB and HIV-1 adult patients receiving the same Vemlidy® dosing regimen.

Table 1. Exposure Comparison of CHB Pediatric and CHB Adult Subjects using NCA Approach

PK Parameters	Mean (CV%) Exposure based on Noncompartmental Analysis					
	Cohort 1 (n=13)		Cohort 2 Group 1 (n=5)		CHB Adults (n=8) (Reference)	
	TAF[a]	TFV[b]	TAF	TFV[c]	TAF	TFV
AUCtau (ng*h/mL)	254 (36.4)	203 (27.9)	313 (64.8)	246 (23.0)	270 (47.8)	400 (35.2)
C_{max} (ng/mL)	188 (45.0)	15 (23.5)	388 (96.9)	17 (19.6)	270 (63.3)	30 (20.8)
C_{tau} (ng/mL)	-	4.1 (39.5)	-	5 (35.9)	-	10 (39.6)

a, n=11 for AUCtau; b, n=12 for AUCtau and Ctau; c, n=4 for AUCtau and Ctau
Source: Study 1092 CSR for CHB pediatric data; PK data in CHB adult are from intensive PK analyses in Trials 108 and 110 CSRs

Table 2. Exposure Comparison in CHB Pediatric and HIV-1 Adult Subjects using PopPK Model Approach

	GLSM				%GLSM Ratio (90% CI) Test/Reference
	CHB Pediatrics (Test)		HIV-1 Adults (Reference)		
TAF PK Parameter					
Cohort 1 (12 to 18 years old)					
AUCtau (h•ng/mL)	N = 47	176.16	N = 539	178.30	98.80 (84.64, 115.34)
Cmax (ng/mL)	N = 47	123.34	N = 539	144.88	85.13 (66.70, 108.66)
Cohort 2 Group 1 (6 to < 12 years old)					
AUCtau (h•ng/mL)	N = 12	153.01	N = 539	178.30	85.82 (54.58, 134.94)
Cmax (ng/mL)	N = 12	87.73	N = 539	144.88	60.55 (25.62, 143.13)

TFV PK Parameter					
Cohort 1 (12 to 18 years old)					
AUCtau (h•ng/mL)	N = 47	244.06	N = 841	283.86	85.98 (80.89, 91.39)
Cmax (ng/mL)	N = 47	14.16	N = 841	14.79	95.76 (89.49, 102.46)
Ctau (ng/mL)	N = 47	8.24	N = 841	10.30	80.03 (74.75, 85.67)
Cohort 2 Group 1 (6 to < 12 years old)					
AUCtau (h•ng/mL)	N = 12	290.77	N = 841	283.86	102.43 (92.21, 113.79)
Cmax (ng/mL)	N = 12	16.42	N = 841	14.79	111.06 (100.78, 122.38)
Ctau (ng/mL)	N = 12	9.75	N = 841	10.30	94.68 (82.81, 108.27)

GLSM, geometric least-square mean; CI, confidence interval
Source: Applicant's Summary of Clinical Pharmacology document [SEQ 0130]

3.2 Exposure-response analysis

No correlations were identified between TAF or TFV exposure and response for efficacy and safety in 59 CHB pediatric subjects at Week 24.

The Applicant conducted exposure-response (E-R) analyses for efficacy endpoints (including categorical HBV DNA outcome (< 20 IU/mL) and normalized ALT at Week 24) and safety endpoints (including percent change from baseline in spine bone mineral density (BMD), percent change from baseline in whole-body BMD, and maximum increase from baseline in serum creatinine). Based on the PopPK derived exposure quartiles, there is a lack of E-R efficacy and safety relationships. Refer to Section 5.3.3 for additional details. The review team also conducted exploratory E-R analysis (in terms of HBV DNA reduction from baseline against exposure metrics from intensive PK subjects). There is no correlation identified between TAF exposure (AUCtau and Cmax) and HBV DNA reduction from baseline or TFV exposure (AUCtau, Cmax, and Ctau) with HBV DNA reduction from baseline at Week 24. Refer to Section 5.2 for additional details.

Collectively, the findings from E-R safety and efficacy analyses at Week 24 suggest that, across the TAF and TFV exposure ranges observed in 59 CHB pediatric patients receiving 25 mg Vemlidy®, there is a lack of apparent differences in reported efficacy or safety outcomes, and therefore, the results provide additional supportive evidence that a dosage of 25 mg Vemlidy® is appropriate for CHB pediatric patients of 12 to <18 years of age. (b) (4)

3.3 Dosage recommendation in CHB adolescent patients with impaired renal function

The Applicant proposes that Vemlidy® is not recommended in CHB adolescent pediatric patients with estimated creatinine clearance (CLcr) below 15 mL/min. The Applicant's proposal is reasonable based on the review team's assessment summarized below. See Section 5.4 for additional details.

The Applicant did not submit any clinical PK or safety data within this submission in support of the abovementioned recommendation; however, based on the available TAF and TFV PK data from adults, adolescent TAF and TFV PK are anticipated to be impacted (due to renal impairment) to a similar extent as those reported for adult subjects with renal impairment (refer to Vemlidy® USPI). Therefore, the current recommendations of TAF in adults with varying degrees of renal impairment (as outlined in the Vemlidy® label) are deemed reasonable for the adolescents with varying degree of renal impairment.

The review team concludes that the Applicant's proposal of no dosage adjustments for Vemlidy® in CHB adolescent patients with estimated creatinine clearance (by Cockcroft-Gault method) of above 15 mL/min is reasonable.

4 Clinical Pharmacology Related Labeling Recommendations

Clinical Pharmacology related labeling recommendations, as of the date of finalizing this review, are summarized below. See the approved USPI for the final labeling.

In Sections 1 and 2, the labeling changes include the indication and recommended dosage for pediatric patients 12 years of age and older.

In Section 12.3, the following labeling language was recommended to the Applicant for including the steady-state PK data for pediatric subjects ages 12 to <18 years from Study 1092 (Table 7 in the package insert). The Applicant proposed additional minor editorial changes in Table 7, including table title and addition of sample size numbers in the footnote. The Applicant proposed revisions were reviewed and found to be reasonable.

> Pediatric Patients
> Steady-state pharmacokinetics of tenofovir alafenamide and its metabolite tenofovir were evaluated in HBV-infected pediatric subjects 12 to less than 18 years (Table 7).

Table 7. Multiple Dose PK Parameters of Tenofovir Alafenamide and Tenofovir Following Oral Administration of VEMLIDY 25 mg in HBV-Infected Pediatric Subjects Aged 12 to less than 18 Years

Parameter Mean (CV%)	Tenofovir Alafenamide[a]	Tenofovir[b]
C_{max} (mcg per mL)	0.188 (45.0)	0.015 (23.5)
AUC_{tau} (mcg•hour per mL)	0.254 (36.4)	0.203 (27.9)
C_{trough} (mcg per mL)	NA	0.0041 (39.5)

CV = coefficient of variation; NA = not applicable

a. From Intensive PK analyses in Trial 1092 (N=13 except N=11 for AUC_{tau}).

b. From Intensive PK analyses in Trial 1092 (N=12 except N=13 for C_{max}).

5 Appendix

5.1 Bioanalysis

A bioanalytical site inspection was requested for the Study GS-US-320-1092. The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) for the bioanalytical site (b) (4) under this sNDA, BLA (b) (4), and NDA (b) (4). An onsite inspection was not conducted due to the disruption of inspectional activities by COVID-19 global pandemic. The OSIS RRR concluded that the data from the analytical portions of this study are reliable and no objectionable conditions were observed (refer to Bioequivalence Establishment Inspection Report Review dated 06/24/2022 in DARRTS).

The review of bioanalytical method validation and performance reports are summarized in Table 3 below.

Table 3. Summary of bioanalytical method validation and performance for the study GS-US-320-1092

Analyte	TAF	TFV
Method	UPLC-MS/MS	UPLC-MS/MS
Matrix	Human plasma (EDTA K2)	Human plasma (EDTA K2)
Validation report	Provided and acceptable	Provided and acceptable
Performance report	Provided	Provided
Samples analyzed within established stability period	☒Yes ☐No	☒Yes ☐No
Quality control (QC) samples range acceptable	☒Yes ☐No	☒Yes ☐No
Chromatograms provided	☒Yes ☐No	☒Yes ☐No
Accuracy and precision of the calibration curve acceptable	☒Yes ☐No	☒Yes ☐No
Accuracy and precision of the quality control samples acceptable	☒Yes ☐No	☒Yes ☐No
Linearity, ng/mL	1, 2, 20, 50, 200, 500, 900, and 1000	0.3, 0.6, 6, 20, 60, 150, 270, 300
Lower limit of quantification (LLOQ), ng/mL	1	0.3
QC Concentrations, ng/mL	1, 3, 50, 400, and 800	0.3, 0.9, 15, 160, and 240
Recovery of Analyte (%)	103.0	92.4
Freeze/Thaw Stability in Plasma	5 cycles at -20°C and -70°C	6 cycles at -20°C and -70°C
Benchtop Stability in Whole Blood	≥4 hours in an ice bath	≥4 hours in an ice bath
Processed Sample Stability	154 hours at 4°C	190 hours at 4°C
Long-term Storage Stability in Plasma	520 days at -70°C	366 days at -20°C 1092 days at -70°C
Incurred sample reanalysis (ISR)	Acceptable	Acceptable
Overall performance	**Acceptable**	**Acceptable**

Source: Bioanalytical Sample Analysis Report, (b) (4) *Study Numbers of 60-1657A and 60-1657B and Amended Bioanalytical Method Validation Report,* (b) (4) *Study Number of 60-1368*

5.2 Study GS-US-320-1092

Study Design:

The Study GS-US-320-1092 is an ongoing randomized (2:1), double-blind, placebo-controlled, multicenter study evaluating the safety, tolerability, PK, and antiviral activity of TAF administered once daily in treatment-naïve and treatment-experienced adolescent subjects and children with CHB.

This review focuses on the results of an interim Week 24 data for adolescent subjects aged 12 to < 18 years weighing ≥35 kg (Cohort 1) and children aged 6 to < 12 years weighing ≥ 25 kg (Cohort 2 Group 1), who received the adult dosage of TAF 25 mg once daily. Subjects were followed for safety and efficacy for 24 weeks of double-blind treatment. After completion of Week 24, subjects were eligible to roll over to receive open-label TAF 25 mg once daily for a total duration of study treatment of 240 weeks with limited monitoring.

Cohort 1:
Adolescent subjects (12 to < 18 years of age) received either the TAF 25 mg tablet or placebo once daily through Week 24.

Cohort 2 Group 1:
Cohort 2 has 3 groups differing by age and weight, including Group 1 (6 to < 12 years of age and ≥ 25 kg), Group 2 (6 to < 12 years of age and ≥ 14 kg to <25 kg), and Group 3 (2 to < 6 years of age and ≥ 10 kg). Each group consisted of Part A (mandatory intensive PK to confirm the dose) and Part B. Intensive PK data were collected from subjects in Part A to confirm the dose of TAF in each dose group and the remaining subjects were enrolled into Part B once dose confirmation was achieved.

Pharmacokinetic Sampling:
For intensive PK sampling phase, blood samples were collected for TAF and TFV PK analysis. Specifically, samples were collected at pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, and 8 hours post-dose. Intensive PK assessments were not conducted, if dosing non-adherence (not related to AEs) was identified on or prior to the intensive PK visit. In these subjects, intensive PK was attempted again post 3 days following adhered/as-scheduled dosing and no later than 7 days after the study visit.

Baseline Demographics of the subjects with intensive PK:
Thirteen out of forty-seven (13/47) adolescent subjects and five out of twelve subjects (5/12) in Cohort 2 Group 1 had intensive PK collected at either the Week 4 visit, or the Week 8 visit, or the Week 12 visit. Baseline demographic information for these subjects is summarized in Table 4.

Table 4. Baseline demographic data for CHB pediatric subjects with intensive PK

	Cohort 1, n=13	Cohort 2 Group 1, n=5
Median age, years (range)	15 (12–17)	10 (8–11)
Median body weight, kg (range)	54.6 (42.1–66.0)	42.5 (29.4–54.1)
Sex (F/M)	6/7	2/3
Race	White, n=4 Asian, n=8 Other, n=1	White, n=3 Asian, n=2

Source: reviewer compiled this table based on the submitted popPK dataset

Pharmacokinetic Results:

(1) TAF/TFV PK in pediatric subjects:

TAF and TFV steady-state PK parameters following multiple-dose administration of TAF 25 mg once daily in the intensive PK set of Cohort 1 and Cohort 2 Group 1 are presented in Table 5. Given the observed differences in efficacy results between Cohort 1 and Cohort 2, TAF and TFV exposures were compared between these two cohorts. TAF AUCtau and Cmax in Cohort 2 Group 1 were 23% higher and 106% higher, respectively, than those in Cohort 1.

Table 5. GS-US-320-1092: TAF and TFV Steady-State PK Parameters

	Mean (%CV)			
	Cohort 1 (N = 13)		Cohort 2 Group 1 (N = 5)	
PK Parameters	TAF	TFV	TAF	TFV
AUC_{tau} (ng*h/mL)	254.3 (36.4)	202.8 (27.9)	312.5 (64.8)	246.1 (23.0)
AUC_{last} (ng*h/mL)	227.0 (42.6)	96.4 (25.3)	309.4 (65.9)	111.6 (19.1)
C_{max} (ng/mL)	187.8 (45.0)	15.3 (23.5)	387.7 (96.9)	17.4 (19.6)
C_{tau} (ng/mL)	-	4.12 (39.5)	-	5.04 (35.9)
T_{max} (h)[a]	1.0 (0.50, 1.5)	1.5 (1.1, 3.0)	0.50 (0.28, 1.5)	2.0 (1.0, 2.0)
C_{last} (ng/mL)	3.83 (92.3)	10.7 (28.8)	3.92 (89.6)	11.4 (26.5)
T_{last} (h)[a]	4.0 (3.0, 5.0)	8.0 (8.0, 8.0)	3.0 (3.0, 3.9)	8.0 (8.0, 8.0)
$t_{1/2}$ (h)[a]	0.5 (0.4, 0.6)	11.8 (10.1, 13.7)	0.4 (0.4, 0.4)	13.0 (10.6, 14.0)
Vz/F (L)	87.2 (45.4)	2356.1 (34.5)	67.2 (80.0)	1820.8 (7.1)
CL/F (L/h)	112.3 (40.3)	135.5 (37.7)	102.9 (45.6)	106.5 (27.0)

PK Substudy Analysis Set with intensive PK samplings
%CV = percentage coefficient of variation; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; TAF = tenofovir alafenamide; TFV = tenofovir; [a]Median (Q1, Q3)
Source: Applicant's Study 1092 CSR

(2) PK comparison between CHB pediatric and CHB adult patients

Mean TAF AUCtau in the Cohort 1 adolescent patients and in Cohort 2 Group 1 were generally comparable to the mean adult steady-state AUCtau value, while mean TAF Cmax in CHB pediatric subjects were numerically different (~30% lower in Cohort 1, ~44% higher in Cohort 2 Group 1) to the mean Cmax value in CHB adults. In the Cohort 1 and in Cohort 2 Group 1, mean TFV AUCtau, Cmax, and Ctau were generally lower than the respective values in CHB adult patients.

Table 6. TAF/TFV steady-state PK parameters in CHB pediatrics vs. in CHB adults

PK parameters	Mean (%CV)		
	CHB adult*, n=8	Cohort 1, n=13	Cohort 2 Group 1, n=5
TAF			
AUCtau, ng•hr/mL	270 (47.8)	254 (36.4)	313 (64.8)
Cmax, ng/mL	270 (63.3)	188 (45.0)	388 (96.9)
TFV			
AUCtau, ng•hr/mL	400 (35.2)	203 (27.9)	246 (23.0)
Cmax, ng/mL	30 (24.6)	15 (23.5)	17 (19.6)
Ctau, ng/mL	10 (39.6)	4.1 (39.5)	5.0 (35.9)

*Source: *PK data in CHB adults are from intensive PK analyses in Trial 108 and Trial 110 treated with TAF 25 mg QD, per Vemlidy® label information. PK data in CHB pediatrics are from intensive PK analyses in Trial 1092.*

Reviewer Comments:

The review team concluded that the higher TAF Cmax observed in Cohort 2 Group 1 are not considered clinically relevant based on the following:

(1) TAF is a prodrug of TFV. TAF is primarily eliminated by metabolism to TFV by cathepsin A in peripheral blood mononuclear cells (PBMC) and carboxylesterase 1 in hepatocytes. TAF has a short half-life (0.5 hour). Therefore, a transit higher TAF concentration is considered not clinically relevant.

(2) Neither TAF nor TFV exposures has been shown to associate with commonly observed AEs (nausea, diarrhea, vomiting, and GI/abdominal pain), bone and renal toxicities, or change from baseline in lipid values, in subjects administered E/C/F/TAF regimen (refer to NDA-207561 clinical pharmacology review dated 7/10/2015).

In addition, the review team concluded that the lower TFV exposure observed in CHB pediatric subjects are not considered clinically relevant based on the following:

(3) Within the available limited data, there is a lack of apparent visual relationship for TFV exposure and HBV DNA outcome (<20 IU/mL) by study cohorts (Section 5.3.3)

(4) An exploratory analysis suggested that there are no apparent relationships identified between exposures (TAF or TFV) and HBV DNA reduction from baseline. (See Section 5.2).

Refer to Section 5.3.2 for exposure comparison evaluation.

Conclusions:
Overall, based on the evaluation of intensive PK results, the drug exposures of TAF (AUCtau, Cmax) and TFV (AUCtau, Cmax, and Ctau) of Vemlidy® in pediatric subjects of ≥ 6 to <18 years of age who received the 25 mg adult strength tablet have no meaningful differences to the respective exposures in CHB adult patients receiving the same Vemlidy® dosage.

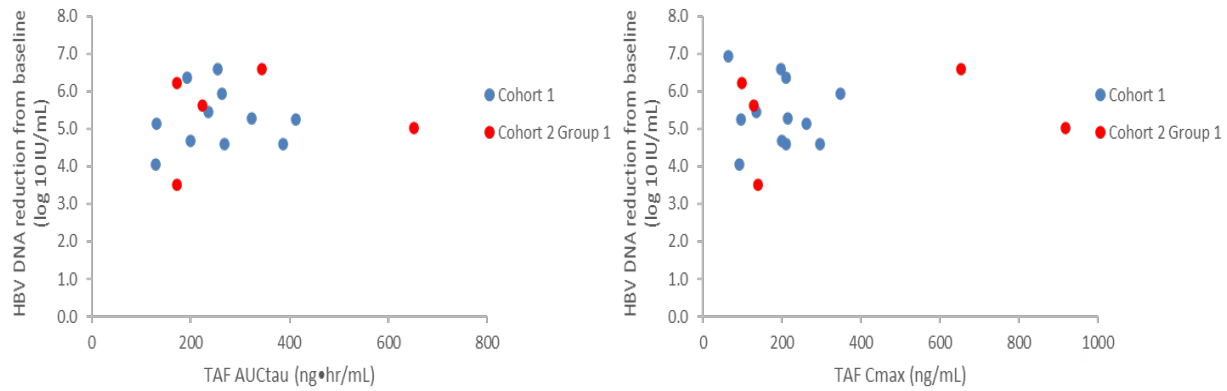
Exploratory Exposure-Response analysis: Relationships between HBV DNA reduction at Week 24 from baseline and exposure metrics from intensive PK subjects

Refer to the section of Pharmacometrics Review for the review team's formal exposure-response analysis on the primary efficacy endpoint (proportion of subjects with plasma HBV DNA levels < 20 IU/mL at Week 24).

The review team performed an additional exploratory exposure-response analysis on HBV DNA reduction at Week 24 from baseline in pediatric subjects of interest, using exposure metrics from intensive PK subjects to evaluate association between DNA reduction and the exposures of TAF and TFV. This exploratory analysis was performed due to the observed discrepancy in efficacy results between the younger (6 to <12 years) and older (12 to <18 years) age cohorts at Week 24. The analysis showed no exposure-related differences in HBV DNA reduction (Figure 1 and Figure 2). Statistical analyses were not conducted due to no visually apparent association observed.

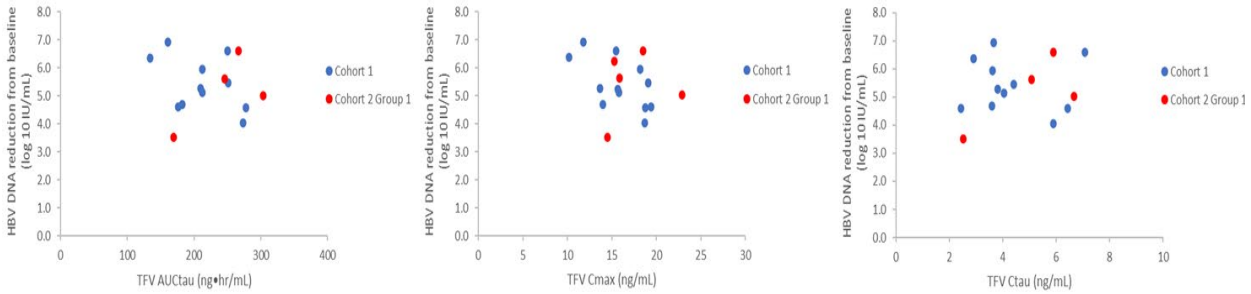
(b) (4)

Figure 1. Exploratory E-R analysis of TAF exposures and HBV DNA reduction from baseline at Week 24 for pediatric patients with intensive PK data



Source: reviewer's independent analysis based on Applicant's NCA derived PK parameters

Figure 2. Exploratory E-R analysis of TFV exposures and HBV DNA reduction from baseline at Week 24 for pediatric patients with intensive PK data



Source: reviewer's independent analysis based on Applicant's NCA derived PK parameters

Conclusion:

Overall, there was no visually apparent relationships identified between exposures (TAF or TFV) and HBV DNA reduction from baseline.

5.3 Pharmacometrics Review

5.3.1 Population PK analysis

Review Summary

The Applicant updated an existing population pharmacokinetic (popPK) model to describe the disposition of tenofovir alafenamide (TAF, prodrug) and TFV (tenofovir) in subjects with chronic hepatitis B (CHB). Several review issues arise regarding selection of reference population, drug exposure estimates, and exposure-response relationships for efficacy and safety. Details are further elaborated in this review. It was noted in the original NDA review of Vemlidy® that the popPK model was not adequate to characterize PK exposure of TAF in CHB adult patients (See the Clinical Pharmacology review; reference ID: 3790589). Following an Information Request for the aforementioned review question and acceptance of this exposure comparison strategy, the review team also focused on the validation of the popPK model analysis of pooling of HIV-1 and CHB pediatric PK data by the Applicant. Despite no known disease state impact on PK, an independent popPK modeling analysis was conducted with CHB pediatric sub-population of interest. This served as an important evaluation step as the popPK model-derived individual exposures of Vemlidy® was used for exposure-efficacy and exposure-safety analyses for CHB pediatric patients. In general, the Applicant's popPK modeling is adequate in characterizing the PK of TAF and TFV and in supporting the exposure-response analyses for efficacy and safety. At Week 24, there was no apparent exposure-efficacy or exposure-safety relationships observed. Collectively, the Applicant's analyses support the dose selection of TAF in pediatric patients with CHB.

Introduction

The primary objectives of the Applicant's popPK analysis were to:

- To update the existing TAF and TAF-TFV popPK analysis with CHB data in pediatric population of interest
- To identify difference in TAF PK, if any, between HIV-1 and CHB infected pediatric patients
- To evaluate the covariate effects on TAF and TFV exposure in pediatric patients
- Support Vemlidy® dosing recommendation in pediatric subjects (b) (4)

Model Development

Data

The popPK analysis was conducted utilizing PK data from 5 studies in children and adolescents, 4 of which were phase 2/3 studies included in an existing popPK model for HIV-1 pediatric patients (PK data from Genvoya®, Descovy®, and Biktarvy®). The current dataset included additional PK data from pediatric patients. A summary of clinical studies is described in **Table 7.** Note that for Study GS-US-320-1092 (herein referred to as Study 1092), all pediatric subjects received 25 mg Vemlidy® in Cohort 1 and Cohort 2. Summaries of covariates of the analysis

population are provided in **Table 8** and **Table 9**. Overall, 396 subjects contributed 2030 TAF samples and 3605 TFV samples for model development.

Table 7. Summary of Studies with PK Sampling Included in Population PK Analysis

Study	Study Design/Population	Treatment	Sampling (Intensive/Sparse)
GS-US-292-0106	A Phase 2/3, Open-Label Study of the Pharmacokinetics (PK), Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen in HIV-1–Infected, Antiretroviral Treatment-Naive Adolescents and Virologically Suppressed Children	Cohorts 1 and 2 (adolescents and children [6 to < 18 years of age, weighing ≥ 25 kg]): E/C/F/TAF 150/150/200/10 mg fixed-dose combination (FDC) Cohort 3 (children ≥ 2 years of age weighing ≥ 14 to < 25 kg): E/C/F/TAF 90/90/120/6 mg FDC	Intensive + Sparse
GS-US-292-1515	A Phase 2/3, Open-Label Study to Evaluate the Safety and Efficacy of E/C/F/TAF in HIV-1–Infected, Virologically Suppressed Adolescents	E/C/F/TAF 150/150/200/10 mg FDC	Sparse
GS-US-311-1269	A Phase 2/3, Open-Label, Multicohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1–Infected Children and Virologically Suppressed Adolescents on a 2-Nucleoside Reverse Transcriptase Inhibitor (NRTI)-Containing Regimen	Cohort 1 (adolescents 12 to < 18 years of age, weighing ≥ 35 kg): F/TAF 200/25 mg or 200/10 mg FDC Cohort 2 Group 1 (children 6 to < 12 years of age, weighing ≥ 25 kg): F/TAF 200/25 mg Cohort 2 Group 2 (children 2 to < 12 years of age, weighing ≥ 17 to < 25 kg): F/TAF 120/15 mg	Intensive + Sparse
GS-US-380-1474	A Phase 2/3, Open-Label Study of the PK, Safety, and Antiviral Activity of the GS-9883/F/TAF) FDC in HIV-1–Infected, Virologically Suppressed Adolescents and Children	Cohorts 1 and 2 (adolescents [12 to < 18 years of age] and children [6 to < 12 years of age]): B/F/TAF 50/200/25 mg FDC Cohort 3 (children ≥ 2 years of age weighing ≥ 14 to < 25 kg): B/F/TAF 30/120/15 mg FDC	Intensive + Sparse
GS-US-320-1092	A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection	Cohort 1: TAF 25 mg Cohort 2 TAF 15 mg	Intensive + Sparse

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FDC = fixed-dose combination; F/TAF = emtricitabine/tenofovir alafenamide; NRTI = nucleoside reverse transcriptase inhibitor
Source: Applicant's PopPK Report, Table 1, page 22-23

Table 8. Summary Statistics of Baseline Continuous Covariates

Covariate	Statistics	GS-US-292-0106 (N = 129)	GS-US-292-1515 (N = 50)	GS-US-311-1269 (N = 36)	GS-US-320-1092 (N = 59)	GS-US-380-1474 (N = 122)	Total (N = 396)
Age (years)	Mean (SD)	10.9 (3.72)	14.8 (1.62)	13.1 (2.35)	13.7 (2.65)	10.8 (3.76)	12.0 (3.61)
	Median [Min, Max]	11.0 [3.00, 17.0]	15.0 [12.0, 17.0]	13.0 [8.00, 17.0]	14.0 [7.00, 17.0]	11.0 [3.00, 17.0]	12.0 [3.00, 17.0]
WT (kg)	Mean (SD)	36.9 (15.8)	54.1 (13.9)	43.1 (9.19)	50.7 (12.1)	37.6 (18.0)	41.9 (16.7)
	Median [Min, Max]	33.1 [14.6, 88.8]	52.2 [35.1, 101]	43.4 [22.0, 62.4]	52.2 [29.0, 87.5]	34.0 [14.1, 123]	40.0 [14.1, 123]
BMI (kg/m^2)	Mean (SD)	17.9 (3.44)	21.3 (4.92)	19.1 (2.33)	20.2 (2.91)	18.6 (5.04)	19.0 (4.20)
	Median [Min, Max]	17.4 [12.4, 31.8]	19.8 [15.5, 38.6]	18.7 [14.0, 25.1]	20.1 [15.5, 29.4]	17.7 [12.6, 45.7]	18.1 [12.4, 45.7]
BSA (m^2)	Mean (SD)	1.19 (0.326)	1.54 (0.211)	1.33 (0.194)	1.48 (0.228)	1.19 (0.333)	1.29 (0.324)
	Median [Min, Max]	1.12 [0.640, 2.03]	1.52 [1.19, 2.13]	1.35 [0.880, 1.71]	1.50 [1.00, 2.11]	1.14 [0.590, 2.37]	1.29 [0.590, 2.37]
BCL_{CRSW} (mL/min/ 1.73 m^2)	Mean (SD)	154 (28.4)	160 (26.2)	162 (31.4)	155 (28.6)	156 (29.0)	156 (28.6)
	Median [Min, Max]	150 [98.6, 284]	158 [102, 223]	157 [108, 236]	151 [89.0, 259]	154 [85.0, 284]	151 [89.0, 259]

BMI = body mass index; BSA = body surface area; BCL_{CRSW} = baseline creatinine clearance derived by Schwartz equation; N = number of participants; TAF = tenofovir alafenamide; WT = baseline body weight
Source: Applicant's PopPK Report, Table 6, page 35

Table 9. Summary Statistics of Baseline Categorical Covariates

Covariate	Category	GS-US-292-0106 N (%)	GS-US-292-1515 N (%)	GS-US-311-1269 N (%)	GS-US-320-1092 N (%)	GS-US-380-1474 N (%)	Total N (%)
Sex	Male	54 (41.9%)	18 (36.0%)	19 (52.8%)	34 (57.6%)	52 (42.6%)	177 (44.7%)
	Female	75 (58.1%)	32 (64.0%)	17 (47.2%)	25 (42.4%)	70 (57.4%)	219 (55.3%)
Patient	HIV-1	129 (100%)	50 (100%)	36 (100%)	0 (0%)	122 (100%)	337 (85.1%)
	HBV	0 (0%)	0 (0%)	0 (0%)	59 (100%)	0 (0%)	59 (14.9%)
Race	White	2 (1.6%)	1 (2.0%)	3 (8.3%)	16 (27.1%)	3 (2.5%)	25 (6.3%)
	Black	105 (81.4%)	49 (98.0%)	15 (41.7%)	3 (5.1%)	84 (68.9%)	256 (64.6%)
	Asian	22 (17.1%)	0 (0%)	1 (2.8%)	37 (62.7%)	29 (23.8%)	89 (22.5%)
	Other	0 (0%)	0 (0%)	17 (47.2%)	3 (5.1%)	6 (4.9%)	26 (6.6%)
P-gp inhibitors	No	97 (75.2%)	50 (100%)	34 (94.4%)	57 (96.6%)	109 (89.3%)	347 (87.6%)
	Yes	32 (24.8%)	0 (0%)	2 (5.6%)	2 (3.4%)	13 (10.7%)	49 (12.4%)
Booster groups	Unboosted	0 (0%)	0 (0%)	14 (38.9%)	59 (100%)	122 (100%)	195 (49.2%)
	COBI	129 (100%)	50 (100%)	0 (0%)	0 (0%)	0 (0%)	179 (45.2%)
	LPV/r	0 (0%)	0 (0%)	22 (61.1%)	0 (0%)	0 (0%)	22 (5.6%)
PPIs	No	126 (97.7%)	50 (100%)	35 (97.2%)	59 (100%)	120 (98.4%)	390 (98.5%)
	Yes	3 (2.3%)	0 (0%)	1 (2.8%)	0 (0%)	2 (1.6%)	6 (1.5%)
H2Ras	No	128 (99.2%)	49 (98.0%)	35 (97.2%)	58 (98.3%)	121 (99.2%)	391 (98.7%)
	Yes	1 (0.8%)	1 (2.0%)	1 (2.8%)	1 (1.7%)	1 (0.8%)	5 (1.3%)

COBI = cobicistat; H2RA = histamine 2 receptor antagonist; LPV = lopinavir; N = number of participants; P-gp = P-glycoprotein; PPI = proton-pump inhibitor; RTV = ritonavir; TAF = tenofovir alafenamide
Source: Applicant's PopPK Report, Table 7, page 36

Base model

After evaluating various absorption models, the base one-compartment TAF model with lag-time, sequential zero- and first-order absorption and first-order elimination was used for covariate model building. In the base model, body weight effect was included on CL and V_C using fixed allometric exponents of 0.75 and 1, respectively, and booster effect was included on F1 and D1. Inter-individual variability (IIV) was included on CL and V_C. Residual variability was modeled using a combined error model. For TFV, the TAF popPK model was used as input for the sequential analysis.

Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), precision of parameter estimation, successful model convergence, and relevant diagnostic plots. In addition, principle of parsimony, stability of model, and interpretability of parameter estimates also guided model selection.

Covariate analysis

Covariate analysis was undertaken for the clinically relevant variables: age, sex, body weight, race, body surface area, body mass index, P-gp inhibitors, background therapy, disease status (HIV-1 vs. CHB), and renal function (described by Schwartz equation). **Table 10** summaries the covariate evaluation for the PK parameters of the base model. For stepwise forward inclusion, a difference in OFV of >6.64 was set for significant covariates at $p < 0.01$. For the backwards elimination step, covariate(s) is dropped with an OFV difference of >10.83 ($p < 0.001$).

For TAF-TFV sequential modeling, CHB infection effect was tested on metabolite CLM/F and V_CM/F and was found to not statistically significant with changes in OFV of <2 and quantified differences of <4% with large RSE (>90%). As such, an existing covariate model of body weight effect on CLM/F, QM/F, V_CM/F, and V_PM/F, booster effect on F, and baseline creatinine clearance on CLM/F was retained.

Table 10. Covariates Evaluated for Final Covariate PopPK Model

Covariate	Time Varying (Yes/No)	PK Parameter		
		CL/F	Vc/F	F1
AGE	No	X	X	
WT	No	X	X	
SEX	No	X	X	
RACE	No	X	X	
BMI*	No	X	X	
BSA*	No	X	X	
P-gp inhibitors	Yes	X		
Background therapy	No	X		X
PAT	No	X	X	
Renal function (BCLCRSW)	No	X		

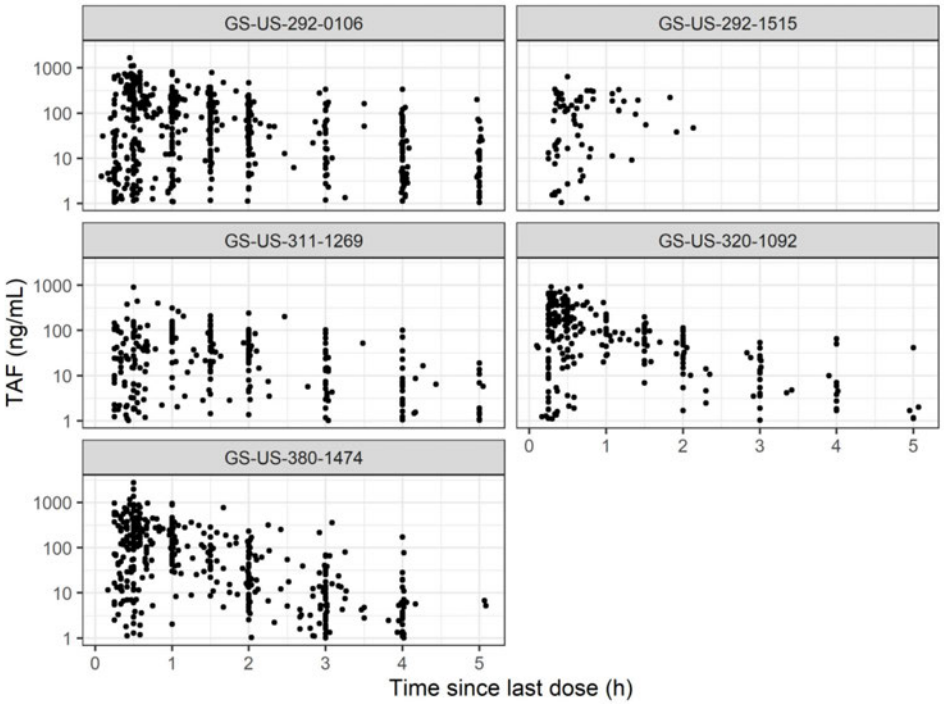
*BCL_{CRSW} = baseline creatinine clearance derived by Schwartz equation; BMI = body mass index; BSA = body surface area; F1 = relative bioavailability of TAF; P-gp = P-glycoprotein; PK = pharmacokinetic(s); PopPK = population pharmacokinetic; TAF = tenofovir alafenamide; WT = baseline body weight; *To be tested if considered relevant*
Source: Applicant's PopPK Report, Table 4, page 30

Final Model

TAF PopPK Model

A total of 396 subjects were included in the final popPK analysis, including 59 subjects with CHB. **Figure 6** depicts the concentration-time profiles by pediatric studies. **Table** 11 and **Table 12** provide a summary of PK parameter estimates of the TAF popPK model and relevant shrinkage values (M3 method was used due to large proportion of BLQ samples for TAF; refer to Applicant's PopPK Report Table 5 for inclusion and exclusion PK samples). **Figure 4** and **Figure 5** provide NPDE summary and prediction-corrected VPC, respectively.

Figure 3. TAF Concentration-time After Last Dose Profiles by Study



Source: Applicant's PopPK Report, Figure 2, page 37

Table 11. PK Parameter Estimates for the Final TAF PopPK Model

Parameter	Parameter Description	Final Model Estimate [RSE][a]	Bootstrap Estimate Median [2.5th; 97.5th Percentiles][b]	SIR Estimate Median [2.5th; 97.5th Percentiles]
$\exp(\theta_1)$	Apparent oral clearance, CL/F (L/h)	112 [23.9%]	94.4 [79.6;123]	113 [95.7;130]
$\exp(\theta_2)$	Apparent central volume of distribution, V_c/F (L)	57.3 [8.9%]	47.4 [33.4;79.3]	57.2 [51.7;62.7]
$\exp(\theta_3)$	First order absorption rate constant, k_a (1/h)	1.99 [1.9%]	1.99 [1.75;2.34]	1.99 [1.92;2.06]
θ_6	COBI effect on F1	1.92 [71.8%]	1.53 [1.32;2.39]	1.93 [1.18;2.81]
$\exp(\theta_7)$	Duration of zero-order absorption, D1 (h)	0.116 [3.8%]	0.11 [0.0503;0.303]	0.116 [0.108;0.124]
θ_8	COBI/LPV/r effect on D1	4.31 [50.2%]	6.35 [1.12;10.2]	4.46 [3.14;6]
$\exp(\theta_9)$	Lag-time (h)	0.0678 [5.1%]	0.00408 [0.00373;0.0777]	0.068 [0.0617;0.0737]
$\sqrt{\theta_4}$	Residual proportional error (%)	98% [0.3%]	96.1 [95.4;100]	98 [97.7;98.3]
θ_5	Residual additive	0.5 [fixed]	0.5 [fixed]	0.5 [fixed]
ω11	IIV of CL/F (%)	81% [10%]	64.8 [62.8;91]	80.8 [76.8;84.8]
ω22	IIV of V_c/F (%)	166% [5%]	147 [147;202]	166 [158;175]
ω21	Correlation CL/F and V_c/F	92% [5%]	58.3 [58;109]	92.5 [89.7;95]

θ = parameter estimate; ω = standard deviation of interindividual variability; COBI = cobicistat; IIV = interindividual variability; PopPK = population pharmacokinetic; RSE = relative standard error; TAF = tenofovir alafenamide

a RSE is defined as the SE divided by the θ × 100% for nontransformed parameters and as SE × 100% for log-transformed parameters.

b Runs with terminated minimization due to rounding errors were included in the calculation of the bootstrap estimates of parameter uncertainty.

Source: Applicant's PopPK Report, Table 13, page 51

Table 12. Shrinkage Estimates for the Final TAF PopPK Model

Parameter	Parameter Description	Shrinkage (%)
$\sqrt{\theta_4}$	Residual proportional error (%)	6.4
ω11	IIV of CL/F	18
ω22	IIV of V_c/F	7.5

θ = parameter estimate; ω = standard deviation of interindividual variability; IIV = interindividual variability; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide

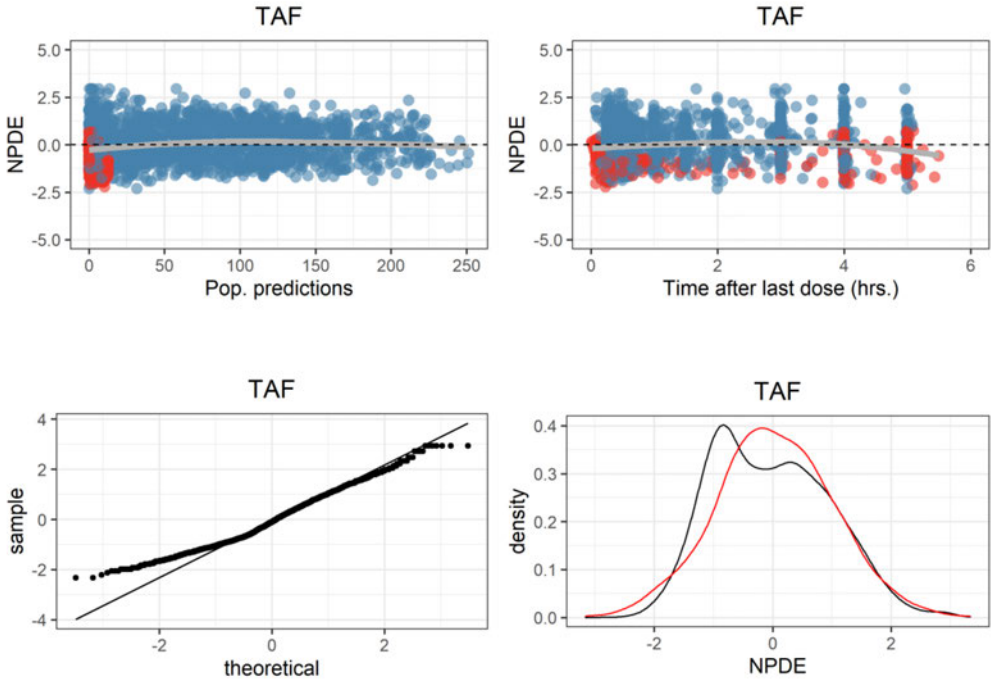
Source: Applicant's PopPK Report, Table 11, page 45

Table 13. NPC of the Final TAF PopPK Model

Criteria	Percent of Observations Meeting Criteria, %
Above the 95th percentile model prediction	4.14
Above the 75th percentile model prediction	25.7
Above the 50th percentile model prediction	49.9
Below the 50th percentile model prediction	50.1
Below the 25th percentile model prediction	28.1
Below the 5th percentile model prediction	0

NPC, numerical predictive check
Source: Applicant's PopPK Report, adopted from Table 12 for CHB population weighing at least 25 kg, page 50

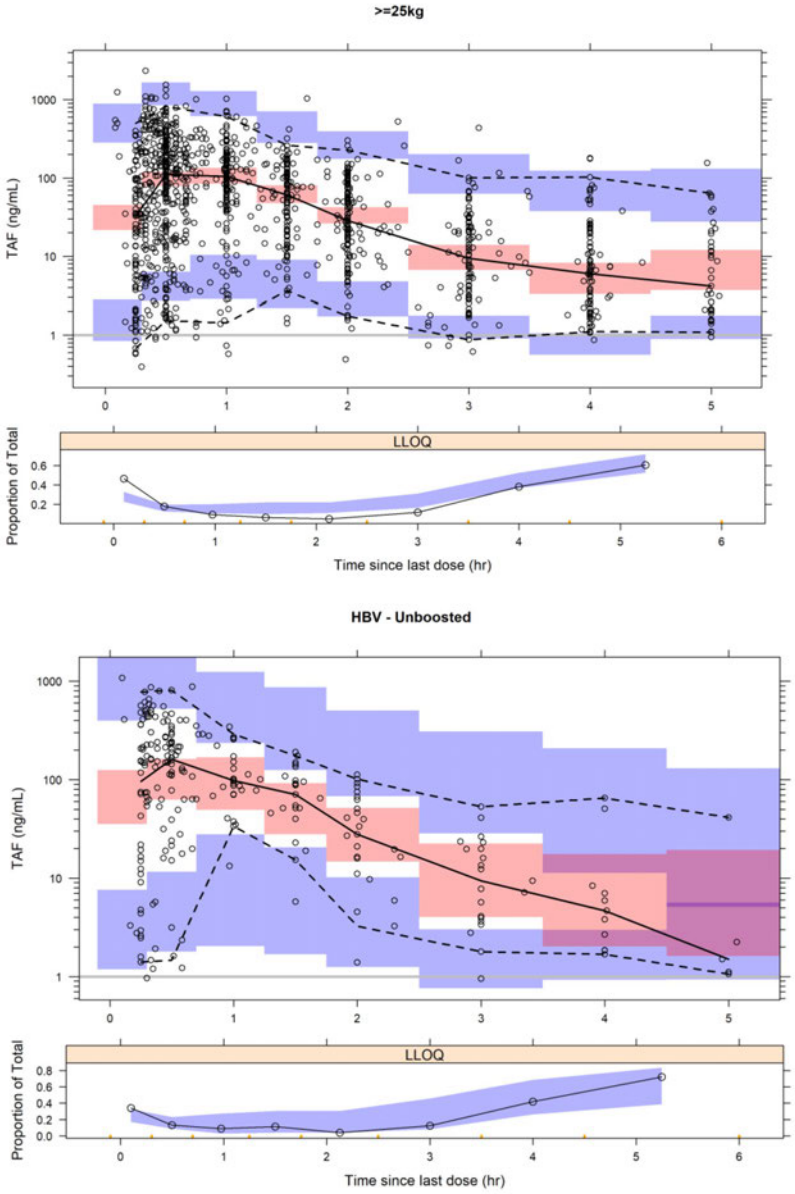
Figure 4. NPDE Plots for the Final TAF PopPK Model



NPDE = normalized prediction distribution errors; Pop. = population; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide
The circles represent individual data points. Blue and red circles represent measurable and BLQ samples, respectively; the gray lines represent loess smooth curves. The black and red lines in the density plot represent density of the NPDE distribution and density of the standard normal distribution, respectively.

Source: Applicant's PopPK Report, Figure 5, page 46

Figure 5. Prediction-corrected VPC of the Final TAF PopPK Model based on Body Weight and Booster Status



CI = confidence interval; LLOQ = lower limit of quantitation; pcVPC = prediction-corrected visual predictive check; the pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the observed concentrations in all participants; the open black circles are the observed data; the red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles
Source: Applicant's PopPK Report, adapted from Figure 6 and 7 for CHB population, page 47-49

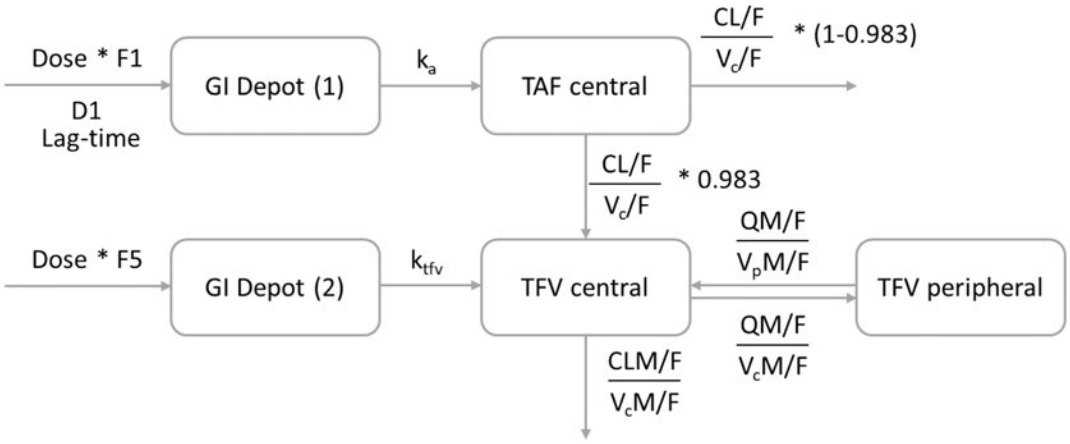
Reviewer comment: Reviewer was able to reproduce the Applicant's final model run. The TAF PK parameters are estimated with reasonable precision (<25% RSE), except that COBI booster on F1 and and D1 were moderate to high (71.8% and 50.2%, respectively); however, Vemlidy® does not contain a booster agent. The inter-individual variability of CL and V_C were high at 81% and 166%, respectively. Shrinkages were low overall (highest at 18%). Although the NPDE diagnostic plots (for the full population) showed a slight trend at lower end of QQ plot, the NPDE results overall indicate no obvious

bias or trends for TAF final model. ETAs of CL and V are centered around around zero (not shown; refer to Applicant's PopPK Report Appendix for diagnostic plots). The pcVPC plots demonstrate a slight overprediction at the absorption phase before approximately 1 hour since last dose; however, the central tendency of the observed TAF data is overall adequately captured for the CHB pediatric population of interest. Additionally, the NPC results demonstrate an overall adequate characterization of the TAF PK data from the final TAF popPK model. In general, the applicant's final TAF popPK model is acceptable for deriving Bayesian posterior predictions and deriving exposure metrics (i.e., TAF AUCtau, Cmax, and Ctau) for exposure-response analyses for CHB pediatric patients (n=59).

TAF-TFV Sequential PopPK Model

A total of 337 subjects contributing 3605 evaluable PK observations were included in the sequential TAF-TFV popPK analysis (scheme shown in **Figure 6**). Only 17 (of 3622) PK samples were excluded total due to BLQ or CWRES greater than 6 (absolute value). Concentration-time profiles after last dose is illustrated in **Figure 7**. Parameter estimates of the TFV PK, as well as the shrinkage estimates, are listed in **Table 14** and **Table 15**, respectively. Diagnostic plots are shown in **Figure 9** and **Figure 9**.

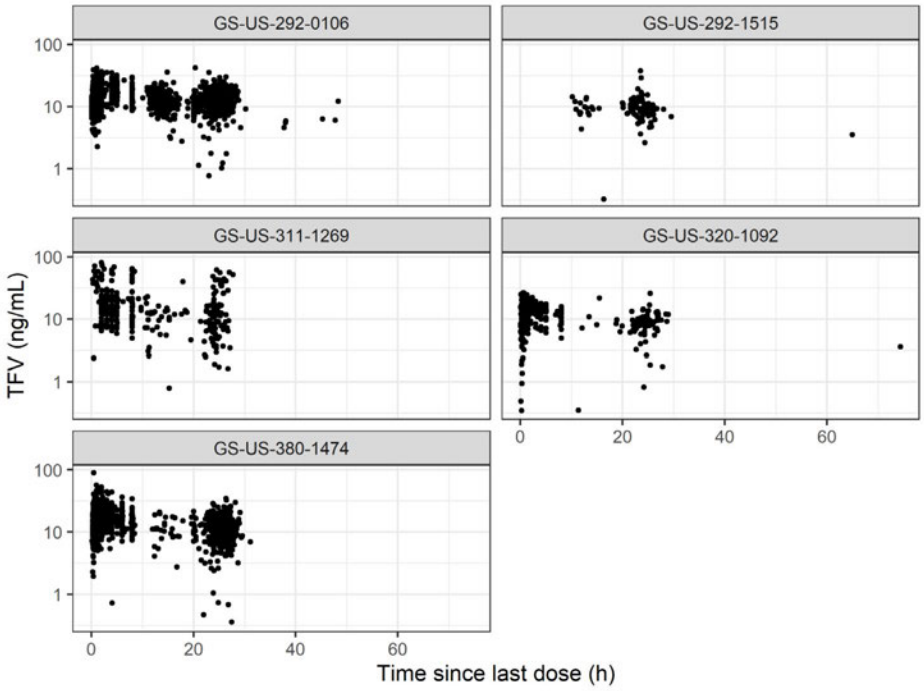
Figure 6. PopPK Model Diagram for TAF-TFV Sequential Model



CLM/F = apparent oral clearance of TFV; k_{tfv} = first order absorption rate constant from second depot compartment; F1 = relative bioavailability of TAF; F5 = relative bioavailability for TFV; GI = gastrointestinal; PopPK = population pharmacokinetic; QM/F = apparent intercompartmental clearance of TFV; TAF = tenofovir alafenamide; TFV = tenofovir; V_cM/F = apparent central volume of distribution of TFV; V_pM/F = apparent peripheral volume of distribution of TFV

Source: Applicant's PopPK Report, Figure 10, page 56

Figure 7. TFV Concentration-time After Last Dose Profiles by Study



Source: Applicant's PopPK Report, Figure 9, page 55

Table 14. PK Parameter Estimates for the Final TFV PopPK Model

Parameter	Parameter Description	Final Model Estimate [RSE][a]	Bootstrap Estimate Median [2.5th; 97.5th Percentiles]	SIR Estimate Median [2.5th; 97.5th Percentiles]
$\exp(\theta_1)$	Apparent oral clearance, CLM/F (L/h)	130 [1%]	130 [126;134]	130 [127;133]
$\exp(\theta_2)$	Apparent central volume of distribution, V_cM/F (L)	2790 [10%]	2780 [2120;3270]	2770 [2290;3310]
$\exp(\theta_4)$	Apparent intercompartmental clearance, QM/F (L/h)	1590 [14%]	1560 [1240;2260]	1600 [1270;2090]
$\exp(\theta_3)$	Apparent peripheral volume of distribution, V_pM/F (L)	5280 [8%]	5300 [4560;6160]	5230 [4460;6020]
$\exp(\theta_8)$	TFV first order absorption rate constant from second depot compartment, k_{TFV} (1/h)	0.138 [51%]	0.135 [0.0568;0.412]	0.132 [0.0536;0.335]
θ_7	LPV/R effect on relative bioavailability	2.25 [8%]	2.26 [1.84;2.61]	2.26 [1.9;2.58]
θ_9	BCL_{CRSW} effect on CLM/F	0.604 [16%]	0.603 [0.399;0.773]	0.613 [0.45;0.757]
$\sqrt{\theta_5}$	Residual proportional error (%)	45 [1%]	44.9 [42.2;47.1]	45 [43.3;46.5]
θ_6	Residual additive error	1.26 [19%]	1.25 [0.889;1.63]	1.27 [0.979;1.52]

Parameter	Parameter Description	Final Model Estimate [RSE][a]	Bootstrap Estimate Median [2.5th; 97.5th Percentiles]	SIR Estimate Median [2.5th; 97.5th Percentiles]
ω11	IIV of CLM/F (%)	24 [11%]	24.2 [21.6;27.2]	24.5 [22.3;26.9]
ω22	IIV of V_cM/F (%)	97 [20%]	97 [79.1;120]	99.1 [83.6;113]
ω33	IIV of V_pM/F (%)	32 [54%]	31.2 [10.2;47]	32.1 [11.6;45.1]
ω44	IIV of QM/F (%)	40 [52%]	38.8 [7.92;57.2]	42.2 [24.3;57.4]

θ = parameter estimate; ω = standard deviation of interindividual variability; CLM/F = apparent clearance of TFV; IIV = interindividual variability; k_{tfv} = first order absorption rate constant from second depot compartment; PopPK = population pharmacokinetic; QM/F = apparent intercompartmental clearance of TFV; SIR = sampling importance resampling; V_cM/F = apparent central volume of distribution of TFV; V_pM/F = apparent peripheral volume of distribution of TFV

a RSE is defined as the SE divided by the θ × 100% for nontransformed parameters and as SE × 100% for log-transformed parameters.

Source: Applicant's PopPK Report, Table 19, pages 62-63

Table 15. Shrinkage Estimates for the Final TFV PopPK Model

Parameter	Parameter Description	Shrinkage (%)
$\sqrt{\theta_4}$	Residual proportional error (%)	8
θ_6	Residual additive	8
ω11	IIV of CLM/F	7.8
ω22	IIV of V_cM/F	30.2
ω33	IIV of V_pM /F	73.5
ω44	IIV of QM/F	72.9

ω = standard deviation of interindividual variability; CLM/F = apparent clearance of TFV; IIV = interindividual variability; PopPK = population pharmacokinetic; QM/F = apparent intercompartmental clearance of TFV; TFV = tenofovir; V_cM/F = apparent central volume of distribution of TFV; V_pM/F = apparent peripheral volume of distribution of TFV

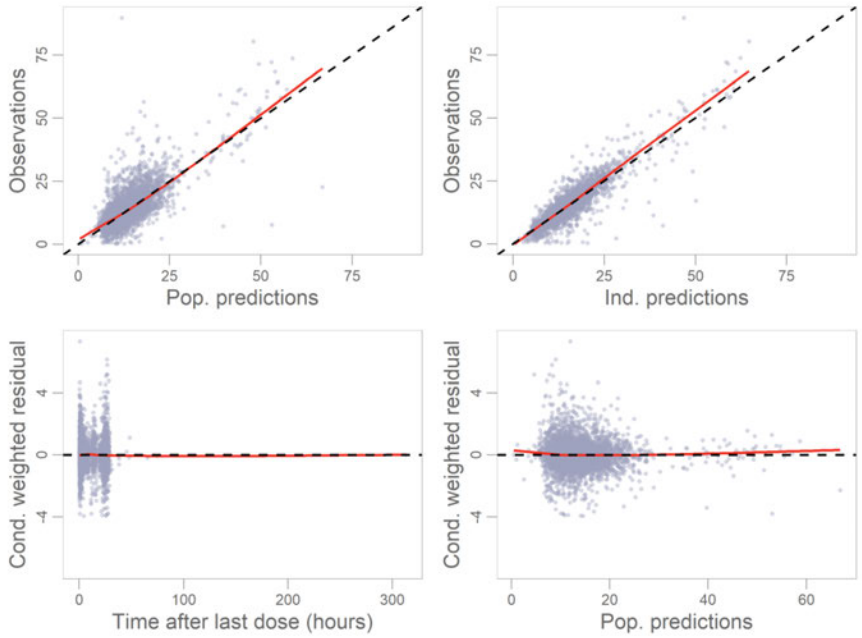
Source: Applicant's PopPK Report, Table 17, page 58

Table 16. NPC of the Final TFV PopPK Model

Criteria	Percent of Observations Meeting Criteria, %
Above the 95th percentile model prediction	5.13
Above the 75th percentile model prediction	25.7
Above the 50th percentile model prediction	55.4
Below the 50th percentile model prediction	44.6
Below the 25th percentile model prediction	18.5
Below the 5th percentile model prediction	3.75

Source: Applicant's PopPK Report, adopted from Table 18 for subjects weighing at least 25 kg, page 62

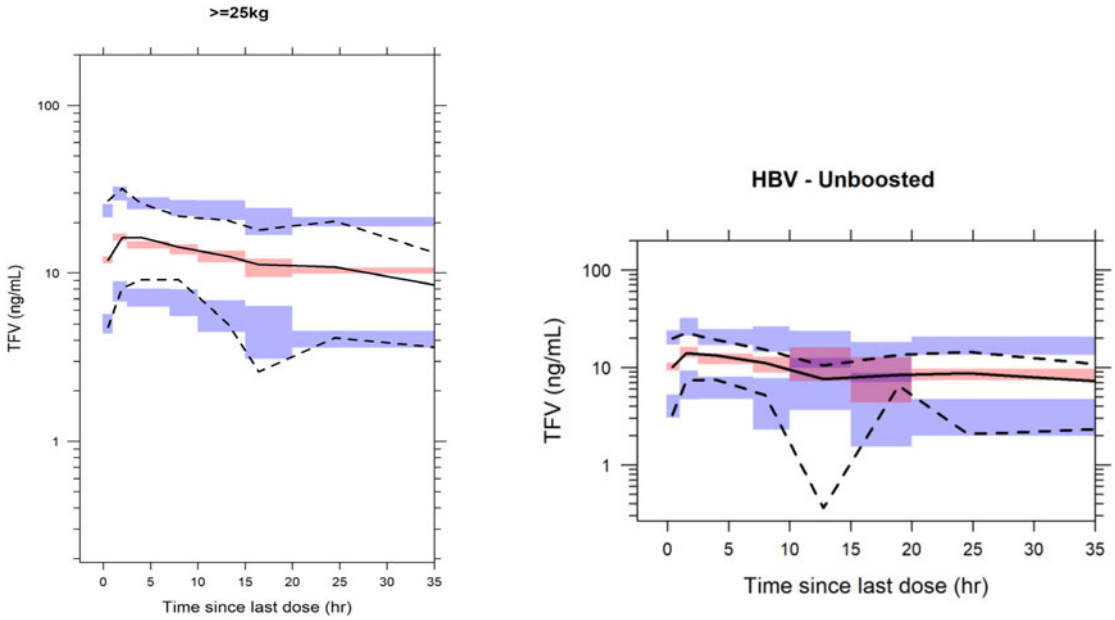
Figure 8. GoF Plots for Final TFV PopPK Model



Cond. = conditional; CWRES = conditional weighted residuals; Ind. = individual; Pop. = population; PopPK = population pharmacokinetic; TFV = tenofovir
The circles represent individual data points; the red lines represent loess smooth curves; and the dashed lines represent either the line of equality (y = x), or a CWRES of 0.

Source: Applicant's PopPK Report, Figure 11, page 59

Figure 9. Prediction-corrected VPC of the Final TFV PopPK Model based on Body Weight and Booster Status



The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the observed concentrations in all participants; the open black circles are the observed data; the red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles
Source: Applicant's PopPK Report, Figure 12 and Figure 13, pages 60-61

Reviewer comments: The reviewer was able to reproduce the Applicant's final model run, and the final popPK model analysis is acceptable for deriving exposure metrics. The final parameter estimates of the TFV (from sequential TAF-TFV modeling) are relatively precise (<20%) except for k_{TFV} (first order absorption rate constant from second depot compartment), inter-individual variability for V_P/F and QM/F (moderate at 50-54%). Shrinkage percent varies from 7.8% to 73.5%. Inter-individual variabilities are moderate for CLM (24%), V_PM (32%), and QM (40%) but high for V_C (97%). While the pcVPC plots are less than ideal (inconsistent trend of the 5th percentile of observed data between 10 to 15 hrs since last dose), indicating a potential overprediction of the final model, the central tendency is generally. In addition, the NPC results and the standard goodness-of-fit plots indicate an overall acceptable fit of the final TAF-TFV sequential model results. Overall, the final TAF-TFV sequential model is acceptable for deriving Bayesian posterior predictions and exposure metrics (i.e., TAF AUCtau, Cmax, and Ctau), supporting exposure-response analyses for CHB pediatric patients (n=59).

Although no known disease state impact on PK, the reviewer conducted independent PK modeling exercise by partitioning out the CHB pediatric population of interest to demonstrate utility and predictability of the Applicant's popPK TAF model. Refer to Reviewer's Independent Analysis section.

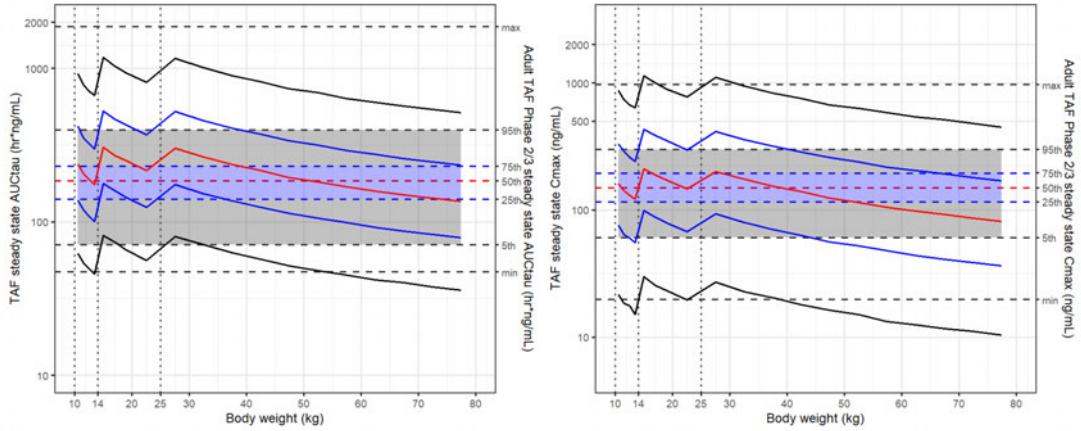
5.3.2 Exposure Comparison to Historical Data

The Applicant utilized the final TAF and TAF-TFV sequential models to derive steady-state exposure of TAF and TFV for the 59 CHB pediatric patients enrolled in Study GS-US-320-1092. The simulated pediatric exposures are compared to an adult reference population exposure (model-derived) with HIV-1 infection who received a fixed-dose combination of elvitegravir/cobicistat/emtricitabine/TAF (Genvoya®). Based on the simulation results illustrated in **Figure 10** and **Figure 11**, the Applicant concluded that simulated pediatric exposures of TAF and TFV (an administered dosage of 25 mg Vemlidy®) are largely contained within the exposure range in the reference population.

Of note, the reference population of a different disease state was pre-specified in Study 1092 Protocol Amendment 4 (reference below), consisting of HIV-1 adult subjects who received 10 mg TAF boosted by cobicistat from Studies GS-US-292-0104 and GS-US-292-0111 in the Genvoya® clinical development program.

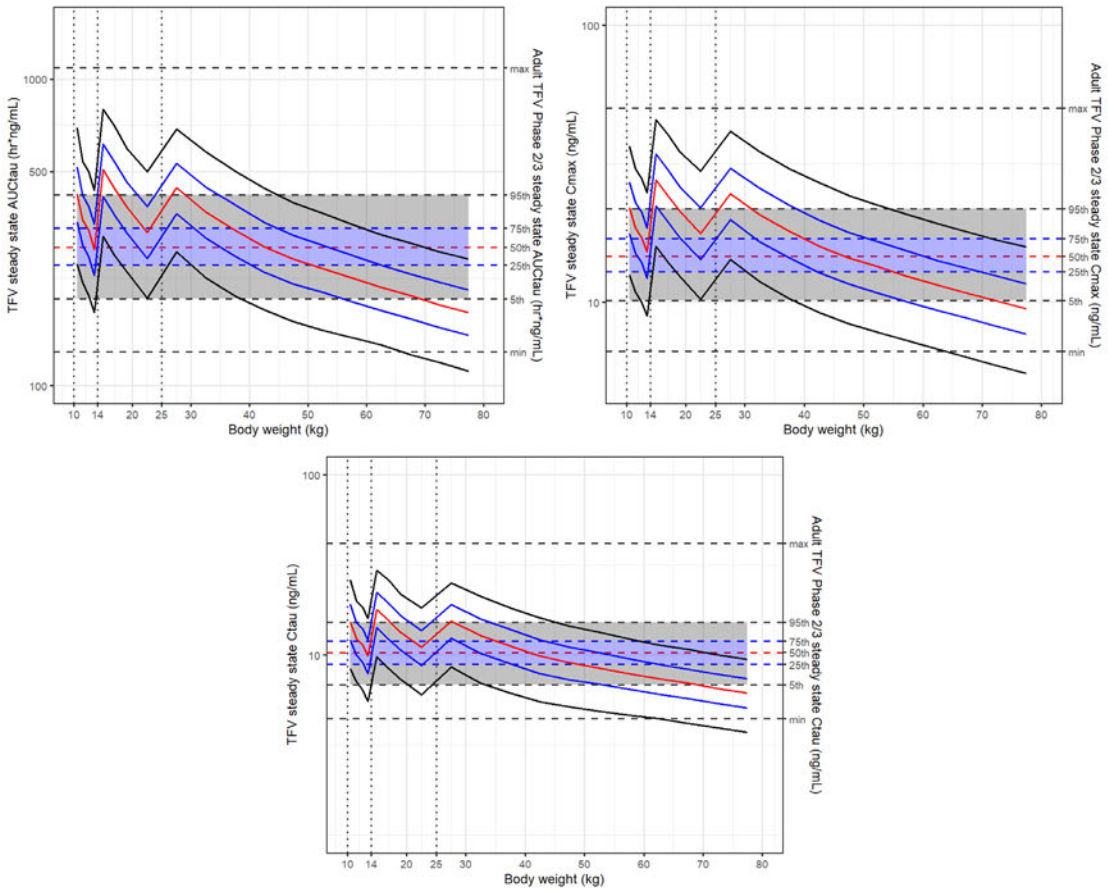
Protocol amendment directory: …\nda208464\0130\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hbv\5351-stud-rep-contr\gs-us-320-1092\protocol.pdf

Figure 10. Simulated TAF AUCtau and Cmax vs. Reference Population



Solid lines *represent the 5th (black), 25th (blue), 50th (red), 75th (blue), and 95th (black) percentiles of simulated pediatric exposures.*
Horizontal dashed lines *represent distribution of adult exposures; vertical dashed lines indicate 10-, 14-, and 25-kg cutoffs; adult exposures are the PopPK-predicted exposures from TAF Phase 2/3 studies; minimum (black); 5th (black), 25th (blue), 50th (red), 75th (blue), and 95th (black) percentiles; and maximum (black) are shown. Blue area shows interquartile range of adult exposure distributions, gray area show 5th to 25th percentiles range and 75th to 95th percentiles range.*
Source: Applicant's Simulation Report, Figure 1, page 13

Figure 11. Simulated TFV AUCtau, Cmax, Ctau vs. Reference Population



Solid lines *represent the 5th (black), 25th (blue), 50th (red), 75th (blue), and 95th (black) percentiles of simulated pediatric exposures.*
Horizontal dashed lines *represent distribution of adult exposures; vertical dashed lines indicate 10-, 14-, and 25-kg cutoffs; adult exposures are the PopPK-predicted exposures from TAF Phase 2/3 studies; minimum (black); 5th (black), 25th (blue), 50th (red), 75th (blue), and 95th (black) percentiles; and maximum (black) are shown. Blue area shows interquartile range of adult exposure distributions, gray area show 5th to 25th percentiles range and 75th to 95th percentiles range.*
Source: Applicant's Simulation Report, Figure 2, page 14

Reviewer comments: based on the simulation output and comparison, the exposure from CHB pediatric subjects is comparable to those of reference adult population; however, the rationale of selection of reference population remains unclear to the review team despite an existing Protocol Amendment of Study 1092 for CHB pediatric subjects. The unclarity is further compounded by the fact that the original NDA 208464 clinical pharmacology review document (Ref ID, 3996881) indicated that the

popPK model for CHB adult population had poor goodness-of-fit and was considered inadequate for describing TAF exposures.

To further clarify the Applicant's approach, an Information Request was sent to the Applicant regarding the rationale in support of the approach of comparing TAF and TFV exposures between CHB pediatric patients and HIV-1 adult patients. The Applicant's response is summarized below (dated 22June2022):

- *The approach was pre-specified in Study 1092 Protocol Amendment 4 and 5*
- *"Genvoya® studies in HIV-1 adults represent the first, extensive dataset of TAF exposures and corresponding safety data obtained, and have therefore served as the reference exposure cohort for TAF and TFV in recent Gilead Studies in pediatric participants living with HIV-1 or CHB"*
- *Similar TAF and TFV exposures in adults were observed between HIV-1 and CHB (**Table 17**) with generally ≤10% difference in exposure metrics*

Table 17. Mean (CV%) Plasma PK Parameters of TAF and TFV Following First Dose of 25 mg TAF QD in CHB and HIV-1 Adults

PK Parameter	GS-US-320-0101 CHB Adults TAF 25 mg (N=10)	GS-US-120-0104 HIV-1 Adults TAF 25 mg (N=8)
TAF		
AUC_{last} (h•ng/mL)	153.0 (41.1)	139.7 (57.8)
C_{max} (ng/mL)	249.5 (45.9)	231.8 (76.8)
TFV		
AUC_{inf} (h•ng/mL)	176.1 (32.8)	195.9 (27.2)
C_{max} (ng/mL)	8.3 (41.6)	6.5 (40.1)
C_{tau} (ng/mL)	2.5 (31.8)	2.4 (23.5)

Note: TAF AUC_{last} is presented for single dose PK instead of AUC_{inf} because TAF concentrations were below level of quantification (BLQ) by ~ 5 hours postdose and utilizing AUC_{last} was deemed a more appropriate measure of exposure assessment.

TAF AUClast is presented for single dose PK instead of AUCinf because TAF concentrations were below level of quantification (BLQ) by ~ 5 hours postdose and utilizing AUClast was deemed a more appropriate measure of exposure assessment
Source: Applicant's Information Request response dated June 22, 2022 [SEQ 0133], Table 1

*To demonstrate comparable exposures in **Table 18**, the reviewer performed a statistical comparison using a mixed effects linear model (subject IDs as random effects) in R (R Core Team; version 3.6.3) with the 'nlme' R package (Pinheiro). The subject level data was extracted from respective clinical study reports (GS-US-320-0101 and GS-US-120-0104). For TAF exposure, the p values were 0.49 and 0.48 for AUClast and Cmax, respectively. For TFV exposure, the p values were 0.41, 0.19, and 0.96 for AUCinf, Cmax, and Ctau, respectively. The reviewer noted that the Applicant excluded one CHB subject in TFV Ctau PK summary with a relatively high observed concentration due to sampling time at 8 hours, which is expected. As such, the reviewer performed the analysis based on such exclusion (n=9 for CHB group in this statistical comparison). Overall, no statistical significance was observed based on statistical analysis of adult subject level TAF and TFV exposure data. A few limitations to consider when interpreting this analysis: 1) limited sample size of 59 subjects, which results in a relatively wide*

90% CI of the geometric mean ratio of each comparison (results not shown), 2) first-dose PK only, and 3) the ability to detect a difference, if any, in this subgroup analysis.

To visually examine the CHB exposure in pediatric vs. historical adult population, the reviewer extracted subject level TAF data from Studies GS-US-320-0108 and GS-US-320-0110. A total of 8 adult subjects underwent intensive PK sampling and were available for comparison (as summarized in the Vemlidy® USPI). As shown in ***Figure 12*** *with TAF (as a representative), AUCtau are generally in range between pediatric and adults subjects while Cmax does not. A summary table of exposures is provided for CHB pediatric and adult subjects in* ***Table 18*** *(refer to* ***Table 2*** *for summary of TFV). As an exploratory measure, however, interpretation of this comparison should take the following into consideration: 1) limited sample size, and 2) methodology of exposure derivation due to lack of a qualified popPK model for CHB adults.*

Reference:
R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.URL https://www.R-project.org/.

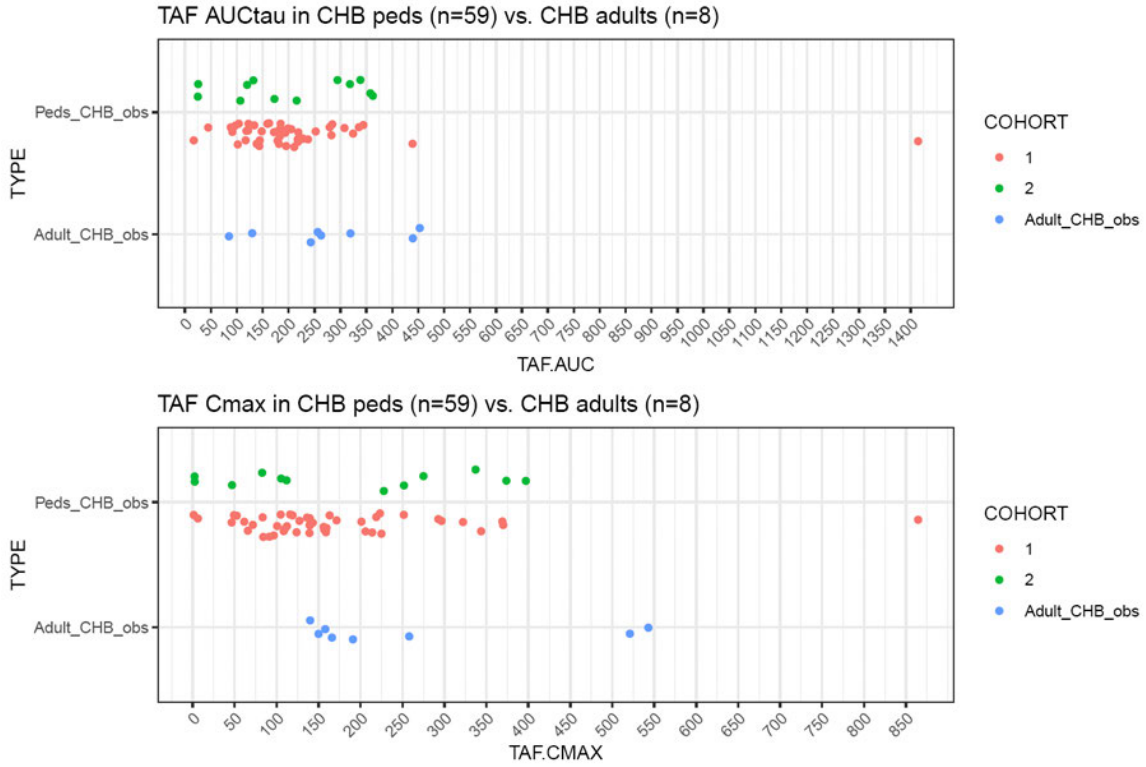
Pinheiro J, Bates D, R Core Team (2022). nlme: Linear and Nonlinear Mixed Effects Models. R package version 3.1-159, https://CRAN.R-project.org/package=nlme.

Table 18. Summary of TAF Exposure

Study	Sample Size	Median AUCtau [CV%] (ng*h/mL)	Median Cmax [CV%] (ng/mL)
CHB Adult	8*	259.37 [47.8]	178.5 [63.3]
CHB Peds	59	183.3 [86.0]	139.3 [80.0]

**Intensive PK only from 320-0108 and 320-0110*
Source: reviewer's independent analysis based on Applicant's submitted data

Figure 12. Model Predicted TAF Exposure in CHB Pediatric Subjects vs. NCA Exposure in CHB Adults



*NCA, noncompartmental analysis; AUCtau, ng*h/mL; Cmax, ng/mL.*
Cohort 1 and Cohort 2 exposure metrics were derived from the Applicant's pediatric popPK model using Bayesian posterior predictions; adult CHB exposures from Studies GS-US-320-0108 and GS-US-320-0110 were derived from noncompartmental analysis
Source: reviewer's independent analysis based on Applicant's submitted data

5.3.3 Exposure-response Analysis at Week 24

The Applicant conducted exposure-response (ER) analysis for efficacy and safety endpoints as shown in **Table 19** for the 59 pediatric subjects (none were excluded). ER relationships were explored as a function of TAF (AUCtau, Cmax) and TFV (AUCtau, Cmax, Ctau) exposure quartiles. A summary of p-values for each ER relationship evaluated is provided in **Table 20**. Although there was a statistically significant association between proportion of subjects with normalized ALT at week 24 and TFV AUCtau (p=0.04, **Figure 13**), the trend is inconsistent with TAF and TFV metrics overall for this efficacy endpoint. Refer to Applicant's Summary of Clinical Pharmacology (SEQ 0130) for graphical representations of ER endpoints not shown in this review. The Applicant concludes that there is a lack of ER efficacy or safety relationships in the current pediatric population with CHB.

Table 19. PK/PD Analysis Endpoints and Sample Size

Analysis Description	Number of Participants Analyzed (N = 59)[a]
PK/PD exposure	59
PK/PD for proportion of participants with HBV DNA < 20 IU/mL at Week 24	59
PK/PD for proportion of participants with normalized ALT (AASLD criteria) at Week 24	59
PK/PD for percent change from baseline in spine BMD at Week 24	59
PK/PD for percent change from baseline in whole-body BMD at Week 24	59
PK/PD for maximum increase from baseline in serum creatinine at Week 24	59

AASLD = American Association for the Study of Liver Diseases; BMD = bone mineral density; HBV = hepatitis B virus; PD = pharmacodynamic(s); PK = pharmacokinetic(s)
a Participants in the PK/PD Analysis Set with available data for analysis of the endpoint of interest

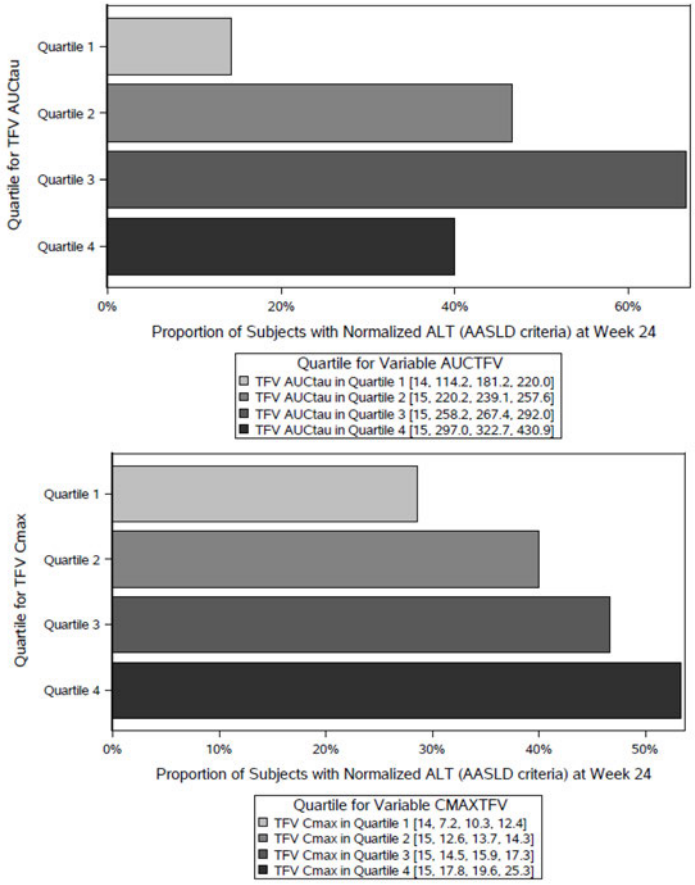
Source: Applicant's Summary of Clinical Pharmacology document [SEQ 0130]

Table 20. Summary of Statistical Significance for ER Efficacy and Safety Relationships

ER Endpoints and P-values at Week 24	TAF		TFV		
	AUCtau	Cmax	AUCtau	Cmax	Ctau
HBV DNA <20 IU/mL	0.9694	0.1665	0.8846	0.8846	0.6024
Normalized ALT	0.1215	0.2996	0.0404	0.6240	0.0983
% Change from baseline in spine BMD	0.8661	0.2866	0.2156	0.5334	0.0551
% Change from baseline in whole-body BMD	0.6338	0.4845	0.2536	0.5675	0.2075
Maximum increase from baseline in serum creatinine	0.9278	0.0775	0.6089	0.4856	0.3594

*ALT normalization based on AASLD criteria; BMD, bone mineral density; HBV, hepatitis B virus; AUCtau, ng*h/mL; concentration, ng/mL; grey box, p<0.05*
Source: adapted from Applicant's Summary of Clinical Pharmacology document [SEQ 0130], section 3.3

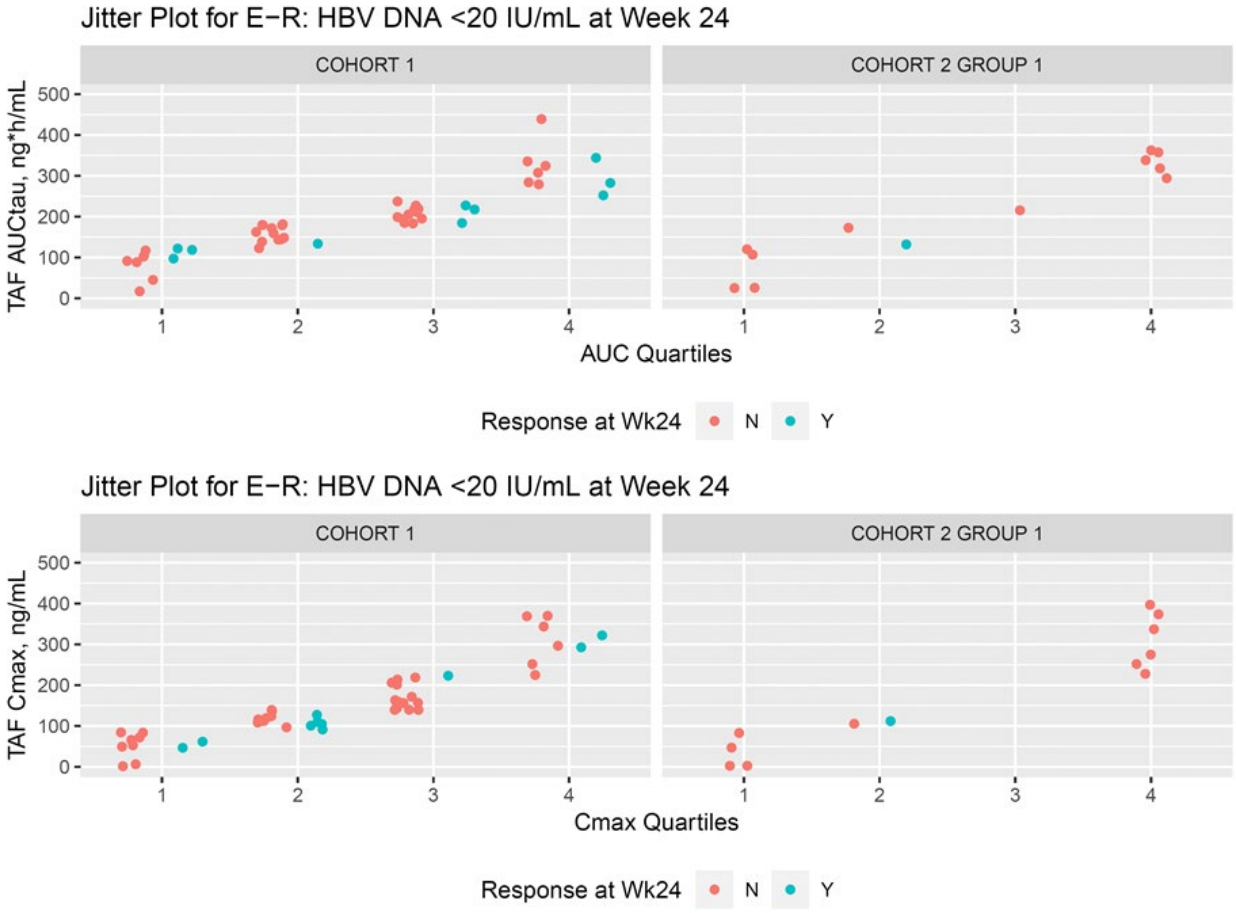
Figure 13. Proportion of Pediatric Subjects with Normalized ALT at Week 24 by TFV AUCtau and Cmax



Source: adapted from Applicant's Summary of Clinical Pharmacology document [SEQ 0130], Figure 12, page 39

Reviewer comments: As an exploratory measure, the reviewer graphically illustrates the ER efficacy relationships by pediatric cohorts (Cohort 1 and Cohort 2 Group 1) based on the interim data. As a representative, the reviewer stratified the AUCtau and Cmax quartiles by study cohorts as shown in ***Figure 14****. There is a lack of apparent visual relationship for TAF exposure and HBV DNA outcome (<20 IU/mL) by study cohorts; however, one might also consider that there is a limited number of study participants, the limited exposure ranges for TAF and TFV from 25 mg TAF, and interim nature of the efficacy data.*

Figure 14. Jitter Plot for TAF ER Efficacy by Response and Study Cohorts



Red data point, non-responders at Week 24; green data points, responders at Week 24
Source: reviewer's independent analysis

5.3.4 Reviewer's Independent Analysis

Introduction

Subletting the CHB pediatric subjects (n=59) from Study 1092 and conduct population PK modeling of TAF via a nonparametric approach

Objectives

Analysis objectives are:

- Characterize TAF PK as an exploratory analysis
- Compare Bayesian posterior-predicted TAF exposures to those derived by the Applicant

Methods

TAF modeling was performed with *Pmetrics* (Neely), an R package with nonparametric adaptive grid algorithm (R Core Team; version 3.6.3) for R. Dataset used (from the Applicant's submission) are summarized in **Table 21.** Row level data was excluded based on the following criteria: exclusion of TFV records, exclusion of dosing records after last PK observation, and retainment of PK observations at or within 5.5 hours post last dose. Dataset was prepared and exported under R (version 3.6.3) with R base functions.

As a formal covariate analysis was conducted by the Applicant (in current submission and previous clinical development programs of other products characterizing TAF PK), the reviewer performed the modeling exercise using a modification of model structure and performed sensitivity analyses with physiological relevant covariates, such as baseline body weight (results not shown). Additive or multiplicative error models were tested to describe residual variability. Predictive performance was assessed using bias (mean weighted prediction error) and imprecision (bias-adjusted mean weighted squared prediction error) in both population and posterior prediction models. The best-fit model was selected based on final AIC or change in -2LL, rule of parsimony, and the goodness-of-fit plots.

Reference:
Neely MN, van Guilder MG, Yamada WM, Schumitzky A, Jelliffe RW. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. Therapeutic Drug Monitoring. 2012; 34(4): 467-476.

R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.URL https://www.R-project.org/.

Table 21. Analysis Data Sets

Datasets	File Name	Link to EDR
Study 1092 TAF PK Data	taf1.xpt	//CDSESUB1/evsprod/nda208464/0130/m5/datasets/ctra-2021-1058/analysis/legacy/datasets
Study 1092 TFV PK Data	tfv1.xpt	//CDSESUB1/evsprod/nda208464/0130/m5/datasets/ctra-2021-1058/analysis/legacy/datasets
Summary of exposure data	adpkpd.xpt [SEQ 0130]	//CDSESUB1/evsprod/nda208464/0130/m5/datasets/pk-pd/analysis/adam/datasets

Results

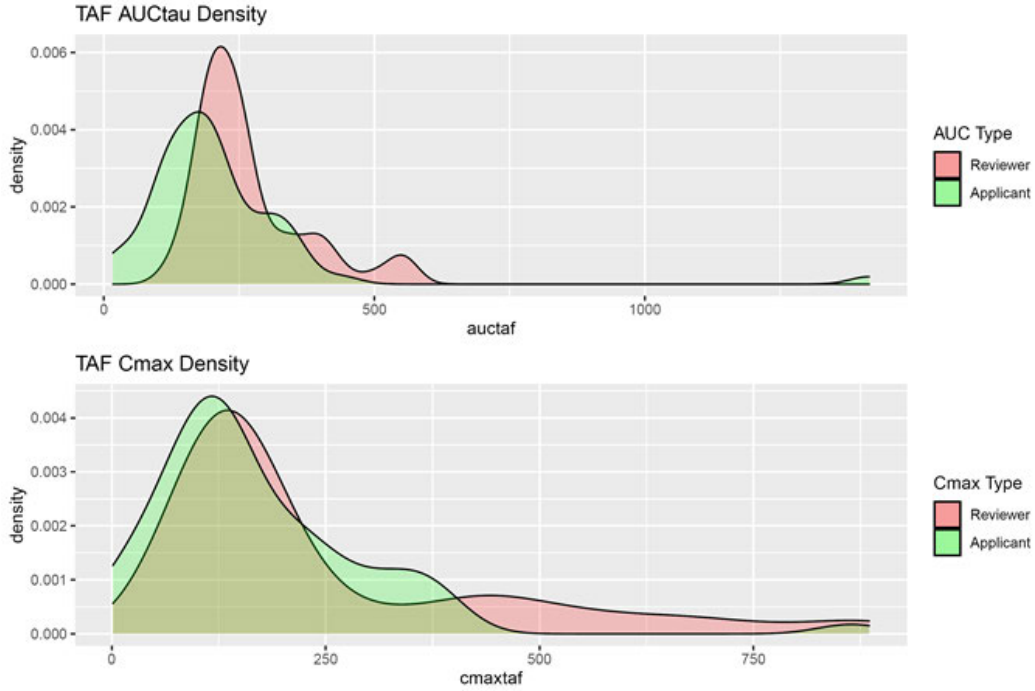
A two-compartment model with absorption constant from input compartment to V_C was selected. Body weight impact (centered to population median of 52.2 kg) was modeled on CL and V_C with allometric scalers of 0.75 and 1.0, respectively. A multiplicative error model was used. A summary of key PK parameters between the Applicant's and the reviewer's models is listed in **Table 22**. A graphical comparison of TAF AUCtau and TAF Cmax is shown in **Figure 15**. Despite partitioning of CHB subgroup in this modeling exercise (with TAF as a representative), the key PK parameters are numerically similar. Furthermore, the density plots demonstrate that the individual TAF AUCtau and Cmax between the two methodologies are also comparable.

Table 22. Summary of Key TAF PK Parameters

PK Parameters	Applicant's TAF Model* (BSV%)	Reviewer's TAF Model (CV%)**
CL (L/h)	112 (81)	101.4 (28.2)
Vc (L)	57.3 (166)	52.4 (60.1)
Ka (h^{-1})	1.99	2.0 (56.8)
Lag time (h)	0.0678	-

**From pooled data of HIV-1 and CHB pediatric subjects*
***CV% derived from support points*
Source: Applicant's results from Applicant's PopPK report; reviewer's independent analysis

Figure 15. TAF Exposure Comparison



Source: Applicant's results from adpkpd.xpt; reviewer's results from independent analysis

Listing of analyses codes and output files

Description	File Name	Location in \\cdsnas\pharmacometrics\
NONMEM Model Runs	Final TAF and TAF-TFV model runs reproduced under version 7.4.3 and 7.5	…\NDA_208464_S14_Vemlidy_JIAJUNLIU\PPK_Analysis\runs
R script	rscript.R	…\NDA_208464_S14_Vemlidy_JIAJUNLIU\PPK_Analysis
Rdata for rscript.R (most recent version)	rscript_08182022_b.RData	
Nonparametric modeling of CHB PK data	pmetrics.R	…\NDA_208464_S14_Vemlidy_JIAJUNLIU\PPK_Analysis
Nonparametric modeling runs*	NA	…\NDA_208464_S14_Vemlidy\PPK_Analysis\pm_runs
Individual PK Summary in CHB and HIV-1 adults from Study 0101 and Study 0104	pkcomparison.csv	…\NDA_208464_S14_Vemlidy_JIAJUNLIU\FDA_Reviews\IR\3June2022
Linear model for individual PK Summary in CHB and HIV-1 adults from Study 0101 and Study 0104	PKcomparison_for_IR.R	…\NDA_208464_S14_Vemlidy_JIAJUNLIU\PPK_Analysis

**Pmetrics run 18 from the reviewer's independent analysis was considered the final model for TAF*

5.4 Renal Impairment

TFV is primarily eliminated renally, and the current submission does not include data (safety, efficacy, or PK) from CHB pediatric subjects of 12 to <18 years of age with impaired renal function. In the adult Vemlidy® labeling, Section 2.3 states the following:

> *No dosage adjustment of VEMLIDY is required in patients with estimated creatinine clearance greater than or equal to 15 mL per minute, or in patients with end stage renal disease (ESRD; estimated creatinine clearance below 15 mL per minute) who are receiving chronic hemodialysis.*

For this pediatric supplement, the Applicant did not propose any changes to the labeling language regarding renal impairment; however, TAF and TFV PK in adolescent population are anticipated to be impacted (due to renal impairment) to a similar extent as those reported for adult subjects with renal impairment (refer to Vemlidy® USPI). Therefore, the current recommendations of TAF in adults with varying degrees of renal impairment (as outlined in the Vemlidy label) also apply to the adolescent population.

The review team considers that no dosage adjustment for Vemlidy® in CHB adolescent subjects with CLcr (by Cockcroft-Gault method) down to 15 mL/min is reasonable.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YANG ZHAO
10/17/2022 04:37:44 PM

JIAJUN LIU
10/17/2022 06:35:23 PM

JUSTIN C EARP
10/17/2022 06:51:40 PM

VIKRAM ARYA
10/17/2022 06:56:12 PM
Signing on behalf of Abhay Joshi.